The Lancet · Saturday 2 January 1960

RESPIRATORY FAILURE

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the past decade or so clinicians have been approach- the problems of cardiac and renal failure along ysiological lines, thinking in terms of cardiac output, merular filtration-rates, and so on But they still m curiously reluctant to use physiological lines of ught in the analysis and treatment of respiratory ease We now have many comparatively simple and sonably accurate methods of measuring respiratory ction, and these greatly sharpen clinical diagnosis t many British teachers of medicine either ignore them gether or refer to them as some sort of activity of kroom playboys and not the sort of thing for a good ctical doctor The current clinical approach is still minated by " stony dullness " and " dry sounds " e position is much better in the United States, where a large number of centres adequate physiological estigation of respiratory disease is regarded as normal cedure The writers of the respiratory sections of erican textbooks base their presentation at least as ch on the physiological approach as on the purely rbid-anatomical

erhaps all this is due to the innate conservatism of the d World, but the fault is not solely that of the clinician s also that of the physiologist, because in some British dical schools the treatment of respiratory function is l frozen at the stage of " lung statics "

linically the concept of respiratory failure, while it long been obvious in such gross asphyxial conditions laryngeal obstruction, has had comparatively little ntion in the many other conditions which involve the gs Perhaps too much emphasis has been placed on effect of these conditions on cardiac function, and the ulting varied symptoms have been regarded as cardio- cular rather than respiratory in origin

espiratory failure can be defined simply as that dition in which the amount of oxygen and carbon xide in the blood-stream is altered by an abnormality he respiratory system On the analogy of other systems can recognise a preliminary stage of " respiratory ufficiency " in which blood-gas levels, normal at rest, ome abnormal during exercise

An analysis of the mechanisms of respiratory failure ls naturally into the three zones of respiratory function

Ventilatory Zone

The ventilatory zone is concerned with the maintenance the alveolar gas tensions at such a level as will ensure it pulmonary capillary blood is saturated with oxygen fore it leaves the respiratory portion of the capillary d that it has rid itself of the necessary amount of carbon xide over the tension range 46–40 mm Hg This quires, on the purely mechanical side, appropriate action of the bellows mechanism of the chest and a nfiguration of the airways, in respect of relative ameters, &c, which will ensure a uniform distribution of inspired air Furthermore the general texture of the lungs must be such that an excessive amount of work is not done in distending them. The rate and depth of respiration are regulated by reflex arcs which sense the blood-oxygen tensions (from chemoreceptors principally in the carotid sinus) and the carbon dioxide and pH of the blood passing through the respiratory centre in the medulla Proprioceptive impulses from the lungs and chest wall also play a part in regulating depth and rate of respiration

A variety of physiological measurements are appropriate to the ventilatory zone Of these the most useful give some index of the amount of air that can be moved per unit of time

One of the simplest is the Wright peak expiratory flowmeter (P F.M)† known more familiarly as the " huffer " This is an adaptation of the anemometer used in a meteorological station to indicate the velocity of wind The patient is merely asked to blow out as hard and as fast as he can through this instrument and a needle jumps up to the maximum velocity attained, which in normal adults is of the order of 500 litres per minute (Wright and McKerrow 1959)

There are many other ways of measuring the maximum breathing capacity (M B C), such as by having the patient breathe as hard as he can into a bag of the Douglas type with the mouthpiece arranged so that inspiration is from the external air The precise time of 12–15 such breaths is recorded The volume is then measured in litres, converted to the equivalent volume at 37°C and 760 mm. Hg, and expressed as the volume per minute. In normal adults it is of the order of 150 litres

A lot of useful information about ventilation can be obtained from a simple spirographic tracing, provided the drum can go fast enough to adequately display a single breath If the spirometer is of the type described by Bernstein et al (1952) it can be used for recording the maximum breathing capacity For this purpose the ordinary Benedict-Roth spirometer, which has been a feature of the clinical physiological laboratory for the past thirty years, is quite unsuitable because of the inertia of its moving parts and because its resonance frequency is about 0 5–1 cycle per second, which means that it overswings grossly when the subject breathes rapidly The expiratory flow-rate can be measured from the straight part of the downstroke of a spirogram of a forced expiration, provided the drum speed is fast enough to open up the time base

There is still a place—though not a very large one—for the measurement of the divisions of lung volume, such as vital capacity, inspiratory capacity, and expiratory reserve volume, and also for the measurement of functional residual capacity by the closed-circuit helium-dilution method (McMichael 1939) or the open-circuit nitrogen method (Darling, Cournand, and Richards 1944) From these data the total lung capacity can be calculated These measurements, although often distorted in disease, do not provide very specific help, because the changes are common to a wide variety of disorders

An important aspect of ventilation is the efficiency with which each inspiration is mixed with the pre-existing air in the lungs

Of the various ways of measuring this perhaps the cheapest is to arrange that the patient breathes pure oxygen for seven minutes, by which time a normal person should have reduced the nitrogen content of his expired air to less than 2 5% (Cournand et al 1941) Values of 15–20% are common in seriously impaired distribution

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* The Frederick Price lecture given to the School of Physic, Trinity College, Dublin, on Nov 24, 1959

† Made by Airmed Ltd, 16, Wigmore Street, London, W 1

Undoubtedly the most convenient method at present available is the single-oxygen-breath procedure, in which, with the aid of a nitrogen meter, a record is made of the nitrogen content of the expiration immediately after a maximal inspiration of oxygen (Comroe and Fowler 1951) In the normal person, as soon as the dead-space gas consisting of pure oxygen is expired, the nitrogen content rapidly climbs to a plateau which is very nearly flat at any rate its slope is no more than equivalent to 1 5% of nitrogen increase from the 750 ml to the 1250 ml levels of expiration Defective distribution of air is indicated by replacement of the plateau by a gentle ascent terminating with gas which has so much nitrogen in it as to show that comparatively little of the maximum breath of oxygen has penetrated to that part of the lung

Diffusion Zone

Oxygen and carbon dioxide have to cross the thin layer of fluid and endothelium which separates alveolar gas and capillary blood Normally this is only about 2 μ thick The rate at which gas traverses this pathway is governed by the difference in tension at the two extremities, the length of the pathway, and the specific solubility and diffusibility of the gas concerned In this respect normal gaseous exchange requires the absorption of oxygen and the elimination of carbon dioxide at a resting volumetric equivalence sufficient to satisfy metabolic demands and to maintain a ratio between the two gases of approximately 5 4 This latter value is set by the overall respiratory quotient of the individual

Since carbon dioxide is much more diffusible (20 1) than oxygen, the normal tension difference of only 6 mm (46–40) between the carbon-dioxide tension of mixed venous blood and that of alveolar air is sufficient to ensure the elimination of an adequate amount In fact the carbon-dioxide tension of the alveolar air and of the arterial blood leaving the lungs is identical This is not true of oxygen, which is so much less diffusible that even at the comparatively high tension difference between 104 mm Hg in the alveoli and 40 mm Hg in mixed venous blood, hæmoglobin is barely saturated by the time it leaves the capillary Even in health, there is a small tension difference (9 mm) between the alveolar air and arterialised blood, although this is partly due to shunting

Estimation of the efficiency of diffusion is essentially by the study of blood-gas levels and their relation to alveolar tensions

The important measurement (Riley et al 1951) is the amount of oxygen passing across the membrane per *millimetre* difference of oxygen tension (diffusion capacity) Technically this is not a very easy measurement because it requires an arterial puncture so that the carbon-dioxide tension of the arterial blood can be measured This is regarded as identical with the carbon-dioxide tension of the alveolar air—from which, and from the exchange ratio, we can calculate the oxygen tension of the alveolar air The oxygen tension of the arterial blood *is* also measured, thus enabling the gradient between alveolus and capillary to be obtained

This is not, however, quite so straightforward as it looks, for part of the difference between alveolar and arterial oxygen tensions is due to the admixture of a certain amount of blood which has bypassed the alveoli or—what comes to the same thing—has passed through imperfectly ventilated alveoli Fortunately Riley et al (1951) with great ingenuity discovered that this admixture factor could be rendered negligible by making the measurements during inhalation of only 14% oxygen It is thus possible to measure the alveolar-capillary gradient due to membrane factor—i e, membrane thickness

There is, however, one desirable measurement which cannot yet be made directly in man and that is the area of the mem- [illegible] A reduction of diffusion capacity by half could theoretically be due to a doubling of the mean thickness alveolar-capillary pathway or a halving of the area alveolar-capillary interface Fortunately, in practice, not usually a serious difficulty, because collateral often indicates which of those two parameters is at fault. instance, when the patient has a collapsed lung or has lung tissue removed, a reduction in diffusing obviously due to loss of area

There are other methods of measuring diffusing capacity, notably the carbon-monoxide-single-breath method, which in outline, consists in measuring the amount of carbon monoxide absorbed from a single breath held for ten seconds (Krogh 1914–15, Bates and Christie 1950) The affinity hæmoglobin for carbon monoxide is so high that for all practical purposes the carbon-monoxide tension of pulmonary capillary blood can be taken as zero Therefore the gradient is simply the *mean* carbon-monoxide tension of the alveolar air This method, however, does not provide for estimation of the admixture factor

The foregoing diffusion tests are admittedly beyond the scope of any but a specialist laboratory. Fortunately a lot of useful clinical information can be obtained from the measurements of the blood tensions of oxygen and carbon dioxide

The normal person has an arterial-blood oxygen saturation of 95%, the difference between that and 100% being due chiefly to the normal amount of alveolar shunting. Abnormal oxygen unsaturation of arterial blood, if severe enough, will lead to visible cyanosis, although it must be remembered that the shape of the curve relating the oxygen content of hæmoglobin to the oxygen tension is such that when cyanosis is actually visible the oxygen tension of arterial blood has dropped 40 or 50 mm Hg. It is wise, if the patient is fit enough, to have him do some mild exercise while the arterial needle is in position; for in many conditions, whereas oxygen saturation is normal at rest, it falls markedly on exercise Now, in the absence of gross shunting, arterial unsaturation is due to one of two factors—either a ventilatory defect lowering alveolar oxygen tension (as in ventilatory insufficiency) or severe loss of diffusion capacity (as in alveolar-capillary block) If, however, at the same time the carbon-dioxide tension of the arterial blood be measured, then these two causes of unsaturation can be sharply differentiated If poor alveolar ventilation be the cause, then, just as the oxygen tension of alveolar air is too low, so will the carbon-dioxide tension be too high—because, as it must be eliminated, it will accumulate in the plasma until it attains the 6 mm ascendance over alveolar carbon-dioxide tension necessary for escape Therefore, anoxia plus hypercarbia means ventilatory insufficiency On the other hand, in alveolar capillary block, carbon dioxide, owing to its high diffusibility, still diffuses out at normal tensions Indeed, the hyperventilation may actually wash carbon dioxide out of the blood-stream, leading to an abnormally low arterial tension

The differentiation between those two important types of respiratory defect has been simplified even further by the direct measurement of the alveolar carbon-dioxide tension As Plesch (1909) originally pointed out, and as Collier (1956) and Campbell and Howell (1958) have emphasised, the carbon-dioxide content of expired alveolar air is identical with that of mixed venous blood when the subject has rebreathed to equilibrium with a bag of air The addition of 6 mm to this value can be taken as a good indication of the carbon-dioxide tension of arterial blood A method very useful in routine clinical practice is to have the patient breathe in and out of a bag ing pure oxygen After a minute and a half this bag carbon-dioxide content very close to that of the nt's alveolar gas The bag is then laid aside for a few kes and the patient then breathes in and out of it for y seconds, by which time the carbon-dioxide content e bag is identical with that of the alveolar gas and of ixed venous blood

mation of the carbon-dioxide content can be done ly with an infra-red analyser or somewhat less lly by the Haldane method or any of its modifications procedure promises to be of great value in routine cal work, because it will show an element of hyper- a in many acute states in which it has not been ected (Griggs et al 1958)

Perfusion Zone

The study of this zone consists essentially in measure- nts of flow and pressure in the pulmonary circulation rdiac catheterisation now enables pressures to be asured at all points from the great veins up to the redge" point, when the pressure closely approximates that in the pulmonary veins and in the left auricle. Flow periods of several minutes is measured by dividing the teriovenous difference across the lung into the amount of ygen taken up (Fick principle) or by the use of tracer bstances such as Evans blue, Coomassie blue, or radio- tive substances such as ^{24}sodium or ^{131}iodinated bumin

As regards pulmonary pressures, hypertension is the sual defect. It is due to physical reduction of the vascular d (as in emphysema), or obstruction of the vessels (as in ultiple pulmonary embolisation), or low oxygen tensions s in long-continued hypoventilation) (Cournand 1950) many slowly progressive pulmonary disorders the ypertension may not be apparent at rest but is obvious during exercise The normal pulmonary vascular bed can ccommodate a several-fold increase in flow with only a light elevation of the pressure. However, when vessel walls are diseased or the oxygen tension of the inspired air s low, the same increase in flow causes very pronounced ypertension. This illustrates the great value of "testing under load", which is in many respects of much greater mportance than merely ascertaining resting values (Riley t al. 1948)

Ventilation-perfusion ratio

A consideration of the combined influence of ventila- tion and perfusion leads to the important concept of the ventilation-perfusion ratio (Riley and Cournand 1949) It has always been clear that the proportion of carbon dioxide eliminated to oxygen absorbed—i e, the respiratory quotient—for the whole body is determined by the metabolic behaviour On an average mixed diet this ratio is 0 8

Thus the proportion of ventilation to perfusion in the lungs must be set so as to effect this exchange This does not, of course, mean that each alveolus must have precisely the same exchange ratio, but the mean level of all alveoli must conform If the whole lung, a lobe of a lung, or a single alveolus is hyperventilated, then an abnormally great quantity of carbon dioxide is eliminated but very little extra oxygen can be taken up that is to say, the exchange ratio is greater than unity On the other hand if ventilation be subnormal, or—what comes to the same thing—perfusion is disporportionately great, then the elimination of carbon dioxide will be reduced more than the absorption of oxygen This situation is seen in its most extreme form when an airway is completely blocked and the gas exchange is so slight that the bubble comes virtually into gaseous equilibrium with mixed venous blood

It is clear that in many disease conditions this delicate proportion between ventilation and perfusion is disturbed in varying degrees ranging from scattered alveolar dys- function through a lobe or single lung up to disturbance of the whole respiratory system

Lung Mechanics

An important development in the physiology of respiration was an analysis of the mechanics of ventilation by a study of the simultaneous pressure-volume values during a single respiratory cycle (Rohrer 1915) This method is the basis of a mathematical consideration of the function of reciprocating steam engines, internal-combustion engines, and pumps

A force which has to be overcome in ventilation is resistance to stretch of the lungs and chest wall, which during normal respiration behave as an elastic structure in the middle or rectilinear part of its expansion/contraction range This resistance obviously increases with increasing depth of respiration, and if it were the only opposition to respiration a plot on x and y axes of the simultaneous values of pressure and volume of a respiration would yield a straight line the angle of which would be a measure of the resistance of the lung and chest wall to stretch

Other non-elastic forces are developed in moving air through the air-passages and in moving tissue planes over each other These increase with the speed of breathing and disappear altogether for a brief period at the height and depth of respiration. The effect of this non-elastic resistance is to deviate the pressure-volume trace from a rectilinear form. In fact, its normal form is that of an ellipse, the area of which is proportional to the work done in overcoming non-elastic resistance whereas the area of the right-angle triangle of which the long axis of the ellipse forms the hypotenuse is proportional to the work done in overcoming elastic resistance. This type of analysis is proving a useful diagnostic tool, because it differentiates sharply between respiratory disability due principally to airway obstruction and disability due principally to diffuse stiffening of the lungs With airway obstruction the area of the loop is much increased, indeed, it may become roughly circular With stiffening of the lungs, on the other hand, the chief alteration is in the slope of the long axis in the direction which indicates a reduction in change of volume per unit of pressure change—i e, a reduction in what is known technically as the "compliance" (Fenn 1951, Christie 1953)

The measurements for this sort of study are first of all the volume displacement during a breath, which is readily measured with a flowmeter connected to a mouthpiece or by a special lightweight spirometer (Arnott, Butler, and Pincock 1954) Intrathoracic volumes are obtained from a balloon placed in the œsophagus Volume displacements and intraœsophageal pressures give the mechanical behaviour of the lungs alone, but if the subject is enclosed in a Drinker-type respirator and is breathed passively, the pressure changes in the casket compared with the volume displacements give a mechanical picture of the thoracic cage along with the lungs The differ- ence between these two sets of measurements yields a value for the work done, both elastic and non-elastic, in moving the chest walls alone.

Causes of Respiratory Failure

Just as the functional assessment of the respiratory system falls naturally into certain zones, so the diseases impairing respiration can be grouped correspondingly

Ventilatory impairment is due to any process which interferes with the normal function of the bellows mechanism, either in its moving parts or in its control mechanism Probably the commonest causes are those which lead to airway obstruction, such as bronchitis, emphysema, asthma, and tracheal compression There are processes which interfere with the action of the thoracic cage or pleura—e g , kyphoscoliosis, ankylosing spondylitis, gross obesity, injury to the chest wall (either accidental or operative), scleroderma, pleural effusion, thickened pleura, and pneumoconiosis Neurogenic control may be impaired by an intracranial disease (vascular, neoplastic, or traumatic), barbiturate poisoning, paralytic poliomyelitis, polyneuritis, myasthenia gravis, progressive muscular atrophy, porphyria, or muscle-relaxant drugs of the curariform type

Ventilatory function may also be upset temporarily by a psychological crisis such as hysterical overbreathing

Diffusion defects may arise from any condition which interposes on an extensive scale any new material—be it fluid, cellular tissue, or connective tissue—between alveolar air and capillary blood Among such conditions are pulmonary œdema, which leads to both free fluid in the alveoli and fluid separating the alveolar and capillary walls (e g , in chronic left-sided cardiac failure and particularly mitral-valve disease) and also disorders which are associated with a diffuse overgrowth of tissue (e g , sarcoidosis, pneumoconiosis, berylliosis, scleroderma, radiation fibrosis, pulmonary histiocytosis, lymphangitic carcinomatosis, and the peculiar diffuse inflammatory process called the Hamman-Rich syndrome) (Arnott 1959)

Pressure defects arise in any process which impairs the flow of blood through respiratory capillaries In its most extreme form it may be the result of the lodgment of an embolus in the main pulmonary artery—a process which so much interferes with circulation as to cause rapid death On the other hand blockage of a right or left pulmonary artery, by an embolus or surgical treatment, results in surprisingly little functional impairment The vascular bed of the remaining lung, provided it is reasonably healthy, can dilate sufficiently to accommodate the entire blood-flow without any great elevation of pressure When a lung is removed, functional impairment is comparatively slight, but when blood-flow to the lung is greatly reduced though ventilation remains normal, a serious ventilatory defect results which takes the form of a greatly increased dead-space effect Localised vascular disease, such as may be caused by tuberculosis, bronchiectasis, injury, or neoplasm, is not as a rule of serious functional moment, because any disturbance of ventilation/perfusion ratio can be compensated by the normal areas Diffuse vascular disease is an important cause of pulmonary hypertension, and may be due to such processes as multiple embolisation from thrombophlebitis and chorionepithelioma (Bagshawe and Brooks 1959) or may be the reflection of cardiac disease such as mitral stenosis and left-to-right shunting

Pathological Mechanisms

Apart from extrathoracic disease interfering with the central control of respiration, the principal structural effects of disease can be regarded as

(*a*) Airway obstruction

(*b*) *Stiffening of lungs with increase of the diffusion pathway*

(*c*) Reduction of pulmonary vascular bed

The principal functional effects of respiratory disease are

(*a*) Arterial unsaturation with consequent cyanosis and a varying degree of polycythæmia

(*b*) Where alveolar ventilation is subnormal, carbon-dioxide retention occurs, which in time leads to a diminished sensitivity of the respiratory centre to carbon-dioxide and progressive hypercapnia

(*c*) Retention by the body of base (mainly sodium bi order to buffer the retained carbon dioxide, aggravates the hypertension and the œdema

(*d*) Pulmonary hypertension with consequent right hypertrophy and ultimately failure with systemic venous and œdema

In the early stages of respiratory disease these effects become apparent only during exercise instance, until emphysema is advanced, the arterial saturation is normal at rest though it may drop ably during exercise Similarly the pulmonary pressure may be normal at rest for a time but rises abnormally during exercise

Clinical Picture of Ventilatory Failure

The common cause of this syndrome is airway obstru tion resulting from inflammatory reaction of the linin mucosa This is a common consequence of infection (as bronchitis following coryza or influenza), an allerg stimulus (as in asthma), or chemical damage (as in th inhalation of tobacco smoke or *industrial pollution)* Wi this air-passage inflammation there is often emphysem which, whatever its origin, is certainly associated wit faulty air distribution, alveolar hypoventilation, muc distortion of the ventilation/perfusion ratio, a reduce pulmonary vascular bed, and pulmonary hypertension

In recurrent bronchitis—the commonest cause o ventilatory disability—patients tend to show a steady lev of respiratory disability with periodic crises of acut respiratory failure due to respiratory infection, allerg attacks, or severe atmospheric pollution

Respiratory failure is marked by dyspnœa the effort o breathing increases because the airway is obstructed b swollen mucosa and, above all, retained secretions I emphysema is severe *the position* of the thoracic *cage* i mechanically embarrassing Additional factors causin dyspnœa are carbon-dioxide retention, to which th respiratory centre is only partially *acclimatised*, an hypoxia which stimulates the carotid-sinus and aorti chemoreceptors In all severe cases there is cyanosis du to arterial desaturation if not obvious at rest, it is plai after exercise such as a bout of coughing The mos obvious effects of carbon-dioxide retention are principall in the nervous system Here one must admit that ther is not yet any clear separation between the neural effects o hypercarbia and anoxia, but at any rate both processes ar present in respiratory failure of ventilatory origin, and ar responsible for mental confusion which in the past has *been* regarded uncritically as toxic or febrile delirium Th patient is forgetful, and a few questions—" what day o the week is it ? ", " what did you have for breakfast ? " " which *party won the* election ? "—may at once uncove a gross abnormality Such patients tend to be drowsy and the relatives may complain that they fall asleep in the middle of a conversation *Coarse* irregular muscle twitching is usually present and can be clearly seen when the patient stretches out his arms with the wrists dorsiflexed The twitching resembles the " liver *flap* " of hepati failure

The hypercapnia may be associated with an exacerbation of congestive cardiac failure, shown by distended neck veins and gross œdema The extremities are warm, the pulse is full, and the blood-pressure slightly raised (Westlake, Simpson, and Kaye 1955) The *differential* diagnosis of such a state of respiratory failure is greatly helped by the background of the patient Except during epidemics of virulent influenza, the syndrome rarely develops suddenly in a person who has not been obviously

The patients are usually known bronchitics and their attack is precipitated by an infection of the upper y tract, the whole syndrome arising commonly in about a week after the commencement of an attack the prevailing epidemic The circumstances of the should prevent any confusion with attacks of y œdema due to hypertensive cardiac failure, ial ischæmia, or mitral stenosis The respiratory can be conclusively demonstrated by finding unsaturation and raised carbon dioxide in a sample arterial blood Even more simply the determination of alveolar carbon dioxide by the Campbell-Howell will confirm the diagnosis

t hospitals making systematic tests of arterial blood or alveolar carbon dioxide respiratory failure is often unexpectedly, in a substantial proportion of e-aged or elderly people with congestive cardiac lure who have been regarded as victims of coronary scular disease and whose underlying respiratory condi n has been inadequately assessed The effect of giving ch patients pure oxygen may confirm the diagnosis Donald 1949) The elevation of the oxygen tension of the spired air rapidly offsets the alveolar hypoventilation in spect of oxygen, cyanosis is abolished and the patient is on pink and placid—far too placid in fact, for he may k into coma with aggravation of the muscle twitching he rate of respiration decreases and its amplitude is less wing to the insensitivity of the respiratory centre to rbon dioxide, the respiratory drive of such patients epends unduly on the hypoxic stimulus Once this is rrected, ventilation becomes less and carbon-dioxide tention increases—perhaps dangerously

In patients in whom the respiratory element has not en recognised and who have been treated along con ntional lines for cardiac failure, the response to digitalis d diuretics is often very slow, but when the ventilatory sufficiency is corrected the pulmonary pressure falls, nous congestion subsides, and œdema disappears

reatment of Respiratory Failure of Ventilatory Origin

When a patient presents the sort of picture I have scribed, the aim of treatment is to improve alveolar ntilation Antibiotics are necessary for the *infection*, hich is usually important In a severe case full doses of nicillin and tetracycline are useful The removal of cretions can be assisted by a steam tent, which, old-shioned though it may be, is an excellent means of keep g mucus fluid Aerosols may help, and if there is any bronchospasmic element isopropyl-noradrenaline should e included in the aerosol Oxygen should be given, eferably in a tent because such patients do not readily tain a mask or nasal catheter A close watch should be pt for any increasing stupor or convulsions To prevent hese, the period of oxygen breathing may be only forty nutes in the hour, followed by twenty minutes breath g room air, but marked hypercarbia is an indication for re ventilation *not* for less oxygen In ventilatory failure e use of 5% carbon dioxide in oxygen is, of course, mpletely wrong

Ventilation can be stimulated chemically by the use of inophylline (2 5% solution) and nikethamide (25% ution) given in an intravenous drip under the close rsonal supervision of the physician Large doses are ually necessary, and the amount required is that which oduces the required increase in ventilation without (in e case of aminophylline) nausea and vomiting or (in the e of nikethamide) troublesome convulsions Hence the need for a physician to keep his hand continually on the drip-cock (Hugh-Jones 1958)

Sometimes all these measures fail, because of the amount and stickiness of the secretions or because one cannot correct cyanosis without depressing ventilation dangerously The treatment then is tracheotomy so that bronchial secretions can be sucked out and a positive-negative pressure respirator (e g , of Smith-Clark type) can be connected to the tracheal opening This may save a moribund patient (Davidson 1959) Once the whole ventilatory mechanism is under artificial control, the risk of hypercarbia has gone the blood carbon-dioxide tension is likely to revert to normal within an hour or two and the general electrolyte balance should be normal within two or three days The risks of respiratory depressant drugs—particularly morphine preparations—are obvious, although once tracheotomy with artificial respiration is established their depression of the respiratory centre is no longer of consequence

When the role of respiratory failure was first recognised and these active therapeutic measures were introduced it was thought that the improvement might only be transient and would rarely enable the patient to regain anything approaching a useful life But the extent of recovery may be very great, indeed, many patients rescued from an acute attack of respiratory failure have remained in good health indefinitely

Application of the principles I have outlined would considerably improve the outlook in cases of chronic ventilatory defect. With differences appropriate to the causal disease, this picture of ventilatory failure is reproduced in many disorders—all of them having the capacity to cause alveolar underventilation

Some less familiar causes of respiratory insufficiency and failure have been recognised recently

The grossly obese, with weights above 20 st , often have quite severe respiratory inadequacy (Hackney et al 1959) Not only are they dyspnœic on slight exertion but they are often mentally sluggish and drowsy This has been shown to be due to carbon-dioxide retention The defect here is the great weight of the thoracic integument and the high intra-abdominal pressure caused by the massive deposits of fat The expiratory reserve volume is much reduced and the ratio of dead-space air is increased All this leads to defective alveolar ventilation, habituation of the respiratory centre to high pCO_2, and chronic anoxia Polycythæmia, pulmonary hypertension, and ultimately congestive cardiac failure supervene.

Gross thoracic deformity of the kyphoscoliotic type has long been known to terminate sometimes in congestive cardiac failure Recent studies have shown that this is cardiorespiratory failure, the result of alveolar hypoventilation and cor pulmonale It is due to an unusual pattern of breathing which, while it minimises the work and energy required to move the deformed chest, is nevertheless insufficient to secure adequate alveolar ventilation An additional factor in these people is that the pulmonary vascular bed is smaller than normal (Bergofsky et al 1959)

Alveolar-capillary Block Syndromes

As already explained, any process which increases the diffusion pathway so much that it seriously impairs oxygen saturation of hæmoglobin will produce the alveolar-capillary block syndrome Many of the usual causes have been enumerated (Arnott 1959, 1960) The clinical picture varies to some extent according to the causal process, but, provided this is comparatively gradual in its onset (as in sarcoidosis), the first disturbance is dyspnœa This is not the laboured obstructed breathing found in chronic bronchitis or asthma, for the greater ventilatory volume is secured mainly by an increase in the rate rather than the depth of respiration At first this increase is noticeable only on exercise, but, once the disorder is established, the resting respiratory rate is at least 20 per minute, and in the later stages it may be continually as high as 35–40 with little slowing during sleep While still approaching the bedside I have been able to make the diagnosis from the chart, which showed the respiratory rate to have been around 30, with little or no fever, for many days Orthopnœa is absent except when pulmonary hypertension has led to right heart-failure

The cause of this accelerated respiration is probably the generalised stiffening of the lungs, which means that depth of respiration is attainable only by an inordinate expenditure of work From the ventilatory angle the rapid, rather shallow, breathing is inefficient in that it exaggerates the dead-space effect, which reduces alveolar ventilation For a time at least, an increased diffusion pathway can be compensated by an elevation of alveolar oxygen tension, through better ventilation Normally the oxygen tension of room air is about 150 mm whereas that of alveolar air is about 104.

The diffuse stiffening of the lungs has led to the clinical phenomenon which has come to be known as the " door stop " sign This is observed when the patient is asked to take a deep inspiration and the effort is arrested abruptly

I well remember a patient with a diffuse alveolar-capillary disorder in whom bronchoscopy was carried out under general anæsthesia Having inserted a tracheal tube and given a muscle-relaxant drug, the anæsthetist settled down to ventilate the patient by rhythmic contraction of the bag He soon discovered that his compression of the bag was opposed firmly by the indistensibility of the patient's lungs The extensive thickening of alveolar walls which was demonstrated at necropsy some weeks later amply explained this defect

Tachycardia is quite often present From an early stage there is usually some arterial unsaturation, but only when the disease is well established is this sufficient to cause cyanosis, and only in the late stages is the cyanosis evident during rest it can be abolished by raising the oxygen tension of the inspired air Clubbing of the digits is variable in occurrence and is associated with an abnormally large blood-flow in the terminal phalanges, the precise cause of which is unknown Most patients with alveolar-capillary block have a cough, but sputum is usually scanty and non-purulent They usually experience extreme fatigability from an early stage, and by the time arterial unsaturation is substantially at rest they lose weight The general upset depends on pure anoxia without the carbon-dioxide poisoning seen in ventilatory obstruction In this respect the picture approximates to mountain sickness Although oxygen-lack by itself causes headache, anorexia, and some mild confusion with hallucinations, the mental state is usually comparatively clear until near the end—in contrast to cases with ventilatory defects, in which carbon-dioxide retention causes stupor and twitching

Polycythæmia is seldom present—probably because the whole course of alveolar-capillary block is rarely long enough to allow of this adaptation

Clinical examination of the chest usually shows little abnormality other than some moist accompaniments Prolonged expiration and dry sounds of bronchial obstruction are absent As many of the causes of alveolar-capillary block involve the pulmonary vascular bed, pulmonary hypertension with its liability to congestive cardiac failure is often present

The extent and character of radiological changes depend very much on the cause of the syndrome It is important to realise that a patient with a severe degree of block may show virtually no radiological changes, or a diffuse fine mottling Obliteration of costophrenic angles and prominence of fissure lines may be visible

The principal physiological changes are the increased alveolar-capillary gradient with arterial unsaturation and a normal or reduced arterial carbon-dioxide content The alveolar carbon dioxide is also normal or reduced This arterial unsaturation can be fully corrected by inhaling oxygen

A spirogram shows no evidence of obstruction The total capacity and total lung capacity are reduced, almost entirely through curtailment of the inspiratory capacity

Pressure/volume curves of the respiratory cycle show a reduced compliance, as the result of the stiffening of the lungs, with a normal non-elastic component indicating free airways

As the airways are not involved, pulmonary mixing is normal and tests of maximum breathing capacity (such as the peak expiratory flow-rate) give values either low normal or very slightly impaired These values are much better than they would be if the syndrome were due to ventilatory defect

Although the diagnosis of alveolar-capillary block, to be precise, requires considerable cardiorespiratory laboratory resources, a reasonable diagnosis can be made on the basis of dyspnœa, hyperventilation, and tachypnœa, in the presence of diffuse finely dispersed radiological pulmonary lesions and the absence of bronchial obstruction or emphysema The diagnosis will be strengthened if there is post-exercise cyanosis which can be completely abolished by breathing oxygen

There is, of course, a wide range of possibilities as to the disease which may be causing the defect One which I have already mentioned is the curious disorder which has come to be known as the Hamman-Rich syndrome (Rubin and Lubliner 1957) This begins usually as a respiratory-tract infection of the inflammatory type but goes on to develop the clinical picture of alveolar-capillary block leading to death within a few months The alveolar septa are found to be diffusely thickened with young connective tissue, and the alveolar endothelium instead of being extremely thin becomes cuboidal or even columnar

Treatment of the alveolar-capillary block syndrome must be directed at the causal process For instance, the treatment of sarcoidosis with corticoids is often successful, and radiation reaction, provided no further radiotherapy is given, sometimes subsides satisfactorily Unfortunately, many of the causes are irreversible end-stages of disease Anoxia is treated by oxygen inhalation, but where the disease is progressive the patient will become increasingly dependent on his oxygen lifeline There is no physiological objection to oxygen therapy, for, in contrast to cases of ventilatory insufficiency, carbon-dioxide retention is absent Any concurrent factor which causes bronchial obstruction, such as inflammation or hypersensitivity, should be treated appropriately

Conclusion

I hope I have made it clear that order and disorder in pulmonary function (Arnott 1955) can be interpreted on the basis of physical chemistry and that much that was previously obscure thus becomes logical and leads naturally to rational treatment

We have to recognise the importance of respiratory insufficiency in such common conditions as bronchitis, bronchopneumonia, chest-wall injuries, and barbiturate poisoning Informed and intelligent treatment of such disorders will save lives

It is a great pleasure to acknowledge the debt I owe to my colleagues who have tried so hard to guide me in this field, in particular Prof Kenneth Donald, Prof Owen Wade, Prof A L d Abreu, Dr George Whitfield, Dr John Bishop, Dr Peter Harris, and Dr John Butler

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AUTOIMMUNE HÆMOLYTIC ANÆMIA WITH ACUTE RENAL FAILURE DUE TO PHENACETIN AND *p*-AMINOSALICYLIC ACID

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CERTAIN drugs, such as acetylphenylhydrazine, when given to normal subjects in sufficiently high dosage, cause hæmolysis A different kind of drug-induced hæmolysis depends on hypersensitivity to a particular drug or drugs Two mechanisms for this have been described

1 The drug may be adsorbed to the red blood-cells, and, with the drug-erythrocyte complex as antigen, " autoantibodies " are formed which subsequently destroy the patient's erythrocytes in the presence of the drug

2 The erythrocytes, because of an inherent enzyme defect, are sensitive to the hæmolytic action of drugs in doses which are not normally harmful (Beutler et al 1954, 1955, Carson et al 1956)

Harris (1956) was the first to give a complete report of an example of the first mechanism he described a case of sensitivity to the antimony-containing drug, stibophen A similar mechanism has been described in hæmolysis due to such drugs as quinidine (Freedman et al 1956), methoin (Snapper et al 1953), and quinine and phenacetin (Muirhead et al 1958)

The second mechanism is now known to be responsible for the hæmolytic episodes which sometimes follow treatment with primaquine (Dern et al 1954), nitrofurantoin (Kimbro et al 1957), sulphonamides and *p*-aminosalicylic acid (P.A.S) (Szeinberg et al 1957), and vitamin-K substitutes (Zinkham and Childs 1957) and in favism (Szeinberg et al 1957)

We report here the production of hæmolysis and acute renal failure in two patients, of whom one was sensitive to phenacetin and the other to P A S In each case the presence of an " autoantibody " was demonstrated

Phenacetin Sensitivity

Phenacetin was introduced in 1887 as an antipyretic and analgesic agent Despite its widespread clinical use, there are few records of side-effects

Smith (1958) noted that skin eruptions, cyanosis due to the production of sulphhæmoglobin and methæmoglobin, and anæmia were the commonest toxic manifestations In addition he referred to renal damage, indicated by hæmaturia, casts, and occasionally oliguria with azotæmia, but detailed case-reports were not given Wuhrmann and Jasinski (1955) described 35 cases of toxic hæmolytic anæmia after phenacetin ingestion. Females were predominantly affected and an association with pre-existing iron-deficiency anæmia was stressed. The possibility of a sex-linked abnormality of the red-cell-enzyme system was suggested. Marti (1958) recorded anæmia, probably due to hæmolysis, in half of 70 cases of chronic phenacetin overdosage Meischer and Pletscher (1958) found that the mean red-cell life in patients taking 1–2 g of phenacetin daily was diminished (but only to levels which a normal bone-marrow could have rectified)

An exact mechanism of hæmolysis due to phenacetin was not described until Muirhead et al (1958) demonstrated, in a single anæmic patient, a phenacetin-dependent antiglobulin reaction. Phenacetin-induced hæmolysis associated with red-cell enzyme (glucose 6-phosphate dehydrogenase) deficiency has not been reported. Dern et al (1955) showed, however, that red cells from primaquine-sensitive individuals, when transfused into normal subjects are hæmolysed by other drugs, including phenacetin

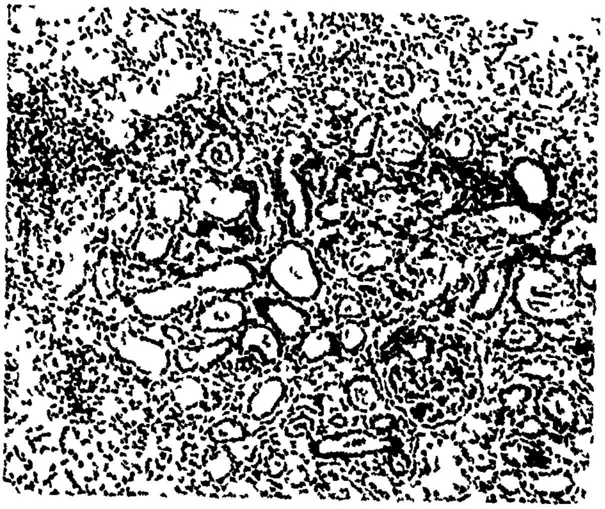
Although the hæmolytic effect of phenacetin has been recognised, acute oliguric renal failure has not been described The kidneys have, however, been reported to suffer damage after prolonged administration Spuhler and Zollinfoe (1953) recorded " primary chronic interstitial nephritis " at necropsy in phenacetin poisoning, and raised the question of renal damage in chronic takers of the drug Lindeneg (1959), too, has correlated chronic renal impairment with long-term phenacetin habituation and suggests that renal papillary necrosis might possibly be caused in this way

CASE ONE

A 38-year-old white woman was admitted to Dartford Hospital in April, 1958, with jaundice and oliguria of 48 hours' duration. 5 months earlier she had had a similar episode, lasting several weeks, with vomiting, malaise, and jaundice but without obvious disturbance of kidney function. Apart from a history of scarlet fever with nephritis at the age of 7 years, there was no evidence of pre-existing renal disease, in particular she had had no nocturia, dysuria, or œdema.

Examination and Investigations

The patient was anæmic, with icterus of the conjunctivæ. No skin rash was noted, and there was no œdema. The spleen was moderately enlarged and both kidneys were palpable The liver was not enlarged.



Case 1: renal biopsy specimen taken during diuretic phase of first illness, showing pronounced interstitial cellular infiltration (× 90.)

Investigation showed a hæmoglobin level of 7·6 g. per 100 ml. and a blood-urea of 233 mg. per 100 ml. In view of this finding and of persistent anuria, the patient was transferred to Hammersmith Hospital for possible treatment by hæmodialysis with an artificial kidney.

Further investigations on admission showed that the hæmoglobin level was unchanged at 7·8 g. per 100 ml., the packed-cell volume (P.C.V.) was 24·5% and the mean corpuscular hæmoglobin concentration (M.C.H.C.) 32%. The leucocyte-count was 4500 per c.mm. and the platelet-count 160,000 per c.mm. The peripheral-blood film showed anisocytosis, with microcytosis, slight polychromasia, and occasional schistocytes. The patient's blood-group was A, rhesus-positive. The total serum-proteins were 7·1 g. per 100 ml., with albumin 3·7 g. per 100 ml. The blood-urea had risen further to 300 mg. per 100 ml., the serum-potassium was 6·6 mEq per litre, with a bicarbonate level of 13 mEq per litre.

Course

Severe oliguria persisted and the patient was treated by a conservative regime for acute oliguric renal failure. The blood-urea reached a peak of 450 mg. per 100 ml. on the 10th day of the illness, at which time a satisfactory diuresis took place. Hæmodialysis was not required, and the subsequent course to recovery was uneventful. The hæmoglobin level did not fall further and was restored to normal by transfusion. Examination of the patient's urine in the diuretic phase, and thereafter, showed no abnormality, and percutaneous renal biopsy revealed the appearances of a recovering tubular necrosis with considerable interstitial cellular infiltration (see figure). There was no evidence of glomerular damage.

Anæmia with tubular necrosis of obscure origin was diagnosed, and the patient returned home after 6 weeks to continue convalescence. For the ensuing 5 months she remained well, the hæmoglobin level was maintained, the blood-urea was normal, and there was no proteinuria. On Oct. 27, 1958, however, she suddenly became ill a few hours after the ingestion of 4 analgesic tablets taken for incipient coryza. The patient stated that her lips and hands became blue and she had a cold sensation in her hands and feet. On the following day she vomited profusely, and voided only a small volume of dark urine. She was observed to be jaundiced, oliguria persisted, and she was readmitted to Hammersmith Hospital.

Readmission

On examination the patient was again anæmic and jaundiced. The kidneys and spleen were enlarged to palpation. Investigations showed a hæmoglobin level of 10·4 g. per 100 ml. and 1·4% reticulocytes. The peripheral-blood film showed slight anisocytosis. No sulphæmoglobin or methæmoglobin was detected, but the serum contained methæmalbumin, and electrophoresis showed absence of haptoglobins (3 days later only a trace of methæmalbumin was present, and the haptoglobins were normal). Osmotic fragility was normal. The plasma-bilirubin (indirect-reacting type) was 1·2 mg. per 100 ml., serum-alkaline-phosphatase was normal, and flocculation tests of liver function showed no abnormality.

Severe oliguria persisted for 10 days, the blood-urea rising to 280 mg. per 100 ml. The protein-anabolic steroid norethandrolone ('Nilevar') was added to the conservative-treatment regime employed during the previous illness, and again hæmodialysis was not required. Following diuresis the patient once more recovered uneventfully, with no evidence of residual renal dysfunction.

Relation of Attacks to Phenacetin

The tablets taken by the patient at the start of the second illness were found to be "A.P.C." and to contain a total dose of 648 mg. of phenacetin. Inquiry established that immediately before her illness in April, 1958, she had taken two 'Veganin' tablets (each containing 250 mg. of phenacetin), and in October, 1957, when she had suffered obscure malaise with jaundice, she recalled having been given two 'Cojene' tablets (each containing 300 mg. of phenacetin). Apart from these three occasions, she denied previously taking any form of analgesic.

It therefore appeared possible that phenacetin was responsible for the episodes of anæmia and acute renal failure. An inherent defect in the patient's red-cell enzymes was first sought as a cause for the sensitivity, but the glutathione-stability test (Beutler 1957) was normal. The direct antiglobulin test, on the other hand, was weakly positive. This suggested that the hæmolysis might be due to an autoantibody mechanism.

The patient's serum was then found to contain a factor which, in the presence of phenacetin but not in its absence, was capable of sensitising normal red cells of the patient's blood-group to agglutination by antiglobulin serum. Further hæmatological studies were then undertaken to define the properties of the serum factor more exactly.

The direct antiglobulin reaction was apparently of the non-γ-globulin type—that is to say, the red cells were agglutinated by an antiglobulin serum to which human γ-globulin had been added. However, when the indirect test was carried out using patient's serum, phenacetin, and normal red cells, the non-γ-globulin reaction was shown to be due to the adsorption of complement. When the test was repeated using heat-inactivated patient's serum and phenacetin it was still positive using the normal antiglobulin reagent (no γ-globulin added) but negative with antiglobulin serum to which γ-globulin had previously been added.

The antibody thus appeared to be potentially hæmolytic in vitro, and this was confirmed by the demonstration that the patient's serum, with added phenacetin, brought about the hæmolysis of trypsinised normal red cells and P.N.H. (paroxysmal nocturnal hæmoglobinuria) red cells in the presence of human serum complement. Hæmolysis of normal (untrypsinised) red cells could not be demonstrated. Normal red cells were, however, agglutinated to approximately the same serum dilutions that produced positive antiglobulin tests (table I).

TABLE I—AGGLUTINATION, HÆMOLYSIS, AND SENSITISATION TO ANTIGLOBULIN SERUM BY ANTIBODY PRESENT IN SERUM OF CASE 1

Cells tested	Dilution of patient's serum			Agglutination and lysis
	1 in 1	1 in 4	1 in 16	
Normal	+ +	±	0	Agglutination (diluent saline)
Normal trypsinised	±	+	0	Lysis (diluent fresh normal serum)
P.N.H.	+ +	+	0	Lysis (diluent fresh normal serum)
Normal (indirect Coombs test)	+ + +	+	0	Agglutination (diluent fresh normal serum)

In each test phenacetin was present at a final concentration of 3·3 mg. per 100 ml.

Readings of agglutination and lysis were made after 2 hours at 37°C.

+ + +, + +, +, ± indicate grades of agglutination and lysis.

TABLE II—SENSITISATION OF NORMAL RED CELLS TO ANTIGLOBULIN SERUM, IN PRESENCE OF VARYING AMOUNTS OF PHENACETIN, BY ANTIBODY PRESENT IN SERUM OF CASE 1

Dilution of patient's serum in fresh normal serum			Final concentration of phenacetin (mg per 100 ml.)
1 in 1	1 in 4	1 in 16	
+++	+±	0	10·0
+++	+±	0	5·0
+++	+	0	2·5
+++	+	0	0·5
+++	±	0	0·05
++	±	0	0·025
±	trace	0	0·005
±	trace	0	0·0025
trace	0	0	0·0005
0	0	0	0·0001

The tests were read after 2 hours at 37°C.
+++, ++, +, ± indicate grades of agglutination.

In all the above experiments control tests using normal serum and phenacetin, patient's serum without phenacetin, and phenacetin alone were set up. No agglutination, hæmolysis, or sensitisation to antiglobulin serum was demonstrated in any of these control tests.

Concentration of Phenacetin and Serum Titre (Table II)

Phenacetin was added to the patient's serum in final concentrations ranging from 10 mg per 100 ml to 0·1 µg per 100 ml. Positive reactions were obtained within the range 10 mg to 2 µg per 100 ml. Employing the antiglobulin reaction as a means of detecting sensitisation the maximum titre of antibody demonstrated was 16.

The antibody at first gained in strength with time. Within a few days of the second hæmolytic episode the maximum titre demonstrated, using the agglutination of normal cells, was 2, 3–4 weeks later it was 8, 7 weeks after the onset of hæmolysis it was 16. The titre had fallen to 2 when serum was tested 9 and 24 weeks later.

Reaction with Other Drugs

Drugs chemically unrelated to phenacetin, but known to be capable of causing hæmolysis by a similar mechanism (e.g., quinidine and methoin), did not, in the presence of this patient's serum, sensitise normal red cells to agglutination by antiglobulin serum. Neither did P.A.S., *p*-aminobenzoic acid, sulphadiazine, procaine hydrochloride, and probenecid. On the other hand, the in-vivo metabolic products of phenacetin—paracetamol ('Panadol') and para-phenetidine—both produced positive reactions. Whereas phenacetin was effective in a final concentration as small as 2 µg per 100 ml, the necessary minimum concentrations of paracetamol and para-phenetidine were 1·7 mg and 1 mg per 100 ml respectively.

P.A.S. Sensitivity

Since its introduction in 1944, P.A.S. has been widely used in the treatment of tuberculosis, and numerous toxic effects have been reported.

The most serious of these have been liver and kidney lesions (Cuthbert 1950, Livingstone and Street 1950, Mann 1953, Cannemeyer et al. 1955, Hensler et al. 1957) and hæmolysis. Renal damage in the absence of other lesions seems rare, but has been recorded (Owen 1958). Derot et al. (1956) reported a case of fatal anuria following the intravenous administration of P.A.S. solution. But, although these workers state that there was no clinical evidence of hæmolysis, no hæmatological investigations are recorded. However, on one occasion before her acute reaction to the final P.A.S. infusion, the patient had had lumbar pain, and the terminal oliguria was preceded by the passage of a few millilitres of red urine. Hæmolysis is a well-known but rare complication of P.A.S. therapy. It has been reported most commonly within 24 hours of taking a small oral dose of the sodium salt of P.A.S. in solution, without previous exposure to the drug (Janet et al. 1951, Tondi 1951, Christiaens and Goudemand 1952, Castanier et al. 1954, Claps 1957, Rowland 1958). Phenolic substances have been isolated from the urine in some of these cases (Christiaens and Goudemand 1952, Castanier et al. 1954, Claps 1957). A direct toxic action on the red cells by some degradation product of P.A.S. has been suggested as the most likely explanation of the hæmolysis. Some experimental evidence in support of this was obtained by Castanier et al. (1956). All but one of a group of rabbits given daily doses of discoloured preparations of the sodium salt of P.A.S. died, while all the controls given unaltered P.A.S. survived.

In some cases acute hæmolysis did not begin until after 15 or more days of treatment with the sodium salt of P.A.S. in solution (Semelaigne et al. 1950) or as tablets (Burkens 1951). In one instance a skin rash was noted at the time of onset of the hæmolysis (case of M. Semelaigne 1950, more fully reported by Christiaens and Goudemand 1952). The delayed type of hæmolysis may have a different pathogenesis, but may only be related to differences in the preparations of P.A.S. employed. Erythrocyte-enzyme defects have been sought in two cases of hæmolysis due to P.A.S. (Szeinberg et al. 1957, Sansone and Segni 1958) and in one (Szeinberg et al. 1957) a low level of reduced glutathione was found. However, no details are given, either about the type of P.A.S. administered or about blood and urine findings at the time of hæmolysis. No immunological mechanism seems to have been described so far for hæmolysis due to P.A.S.

CASE TWO

A 73-year-old man was found to have pulmonary tuberculosis in 1956 and received treatment with 'Pycamisan' (containing P.A.S. and isoniazid) irregularly for an uncertain period. In April, 1959, reassessment revealed persistent active infection, and *Mycobacterium tuberculosis* was cultured from the sputum. The hæmoglobin was 12·5 g per 100 ml and the blood-urea was 44 mg per 100 ml.

On April 23, 1959, a second course of chemotherapy was started using streptomycin 1 g daily, P.A.S. 12 g daily, and isoniazid 300 mg daily. The patient's general condition improved over the next few days. Examination of the urine on April 29, 1959, showed minimal proteinuria and a scanty growth of *Staphylococcus aureus* on culture. There was no pyuria, and the blood-urea remained at 45 mg per 100 ml. No records of urinalysis before the start of chemotherapy are available.

Onset and Course of Hæmolytic Anæmia

On May 7, 1959, after 2 weeks' treatment, the patient became drowsy and anorexic, and the blood-pressure fell to 110/50 mm Hg. The blood-urea had risen to 124 mg per 100 ml although the serum-electrolytes were normal. In consequence the streptomycin was withdrawn. On the following day, the urine was dark brown, it contained more protein than before but no red cells. The hæmoglobin had fallen to 3·9 g per 100 ml.

Hæmolytic anæmia was diagnosed, and the remaining drugs—P.A.S. and isoniazid—were withdrawn. Prednisolone, 10 mg t.d.s., was given in an attempt to control the hæmolysis. During the next 48 hours the patient's condition deteriorated rapidly, the blood-pressure fell profoundly and he was treated with noradrenaline and blood-transfusion. Complete anuria, preceded by oliguria of uncertain duration, was now present, and he was transferred to Hammersmith Hospital for possible treatment by hæmodialysis with an artificial kidney.

On arrival, he was semicomatose with deep respirations. There was a generalised fine macular rash suggesting a drug-sensitivity reaction. The blood-urea had risen to 375 mg per 100 ml, and the serum-bicarbonate level had fallen to 17 mEq per litre. The serum-potassium was 4·5 mEq per litre and serum-bilirubin 6·1 mg per 100 ml. The hæmoglobin was 5·8 g per 100 ml, and methæmalbumin and free hæmoglobin were present in the serum, haptoglobins were absent. The peripheral-blood film showed evidence of autohæmagglutination, and numerous normoblasts were present. There was marked spherocytosis, anisocytosis, and polychromasia. The

TABLE III—AGGLUTINATION, HÆMOLYSIS, AND SENSITISATION TO ANTIGLOBULIN SERUM BY ANTIBODY PRESENT IN SERUM OF CASE 2

Cells tested	Dilution of patient's serum				Agglutination and lysis
	1 in 1	1 in 4	1 in 16	1 in 64	
Normal	+++	+++	+	0	Agglutination (diluent saline)
Normal trypsinised	++	++	trace	0	Lysis (diluent fresh normal serum)
P N H	+++	+++	+±	trace	Lysis (diluent fresh normal serum)
Normal (indirect Coombs test)	+	++	+	0	Agglutination (diluent fresh normal serum)

In each test P A S was present at a final concentration of 40 mg per 100 ml

Readings of agglutination and lysis were made after 2 hours at 37°C.

+++, ++, +, ± indicate grades of agglutination and lysis

reticulocyte-count was 4% Osmotic fragility was increased Bone-marrow aspiration showed erythroid hyperplasia The patient's blood-group was A, rhesus-positive

The renal failure was treated conservatively, but attempts to improve the circulatory state prior to hæmodialysis were unsuccessful and the patient died 30 hours after admission Permission for postmortem examination was not granted

A diagnosis was made of hæmolytic anæmia and acute oliguric renal failure due to one of the three chemotherapeutic agents employed

Further Laboratory Investigations

The glutathione-stability test was normal on admission, but, because this could not be repeated, an inherent enzyme defect could not definitely be excluded as contributing to the drug-dependent hæmolysis, since the population of sensitive cells might have been destroyed in the acute hæmolytic episode As in case 1, however, definite evidence for an autoantibody mechanism was obtained

Serology

The serological findings were similar to those in case 1 The direct antiglobulin reaction was positive, and it was of the non-γ-globulin type Two samples of the patient's serum gave the same results Each sample in the presence of P A S agglutinated normal red cells of the patient's blood-group (titre 16), as well as sensitising them to antiglobulin serum, and also agglutinated and hæmolysed (in the presence of complement) trypsinised normal red cells and hæmolysed P N H red cells (table III) The indirect antiglobulin reaction was almost abolished if the patient's serum was heat-inactivated before sensitisation

The activity of the antibody was dependent on the presence of P A S and could be demonstrated using final concentrations of P A S ranging from 10 mg per 100 ml to 500 mg per 100 ml (the highest concentration tested) No abnormal serum activity could be demonstrated in the presence of isoniazid or streptomycin Drugs chemically related to P A S were next tested Positive reactions were obtained with sodium salicylate and sodium *p*-aminobenzoate, but the results were negative with sodium benzoate, sodium *p*-aminohippurate, salicylamide, procaine hydrochloride, phenacetin, paracetamol, paraphenetidine, probenecid, and sulphadiazine

Discussion

These two cases are thought to represent the second recorded instance of an autoimmune type of phenacetin-induced hæmolytic anæmia, and the first report of such a phenomenon due to P A S The association of renal failure with hæmolysis in both cases suggests that the renal damage was secondary to intravascular hæmolysis This is probable in case 2, but less likely in case 1 because the hæmolysis was mild As renal damage has been described as a toxic effect of both phenacetin and P A S, the drug hypersensitivity in these two patients conceivably led to damage to renal cells as well as to red cells The clinical course in each was that of acute oliguric renal failure, characteristic of acute tubular necrosis from any cause In case 1 renal biopsy in the early recovery phase showed only the changes of healing tubular damage—i e, pigmented casts in the tubules with considerable interstitial cellular reaction (see figure) There was no evidence of a longstanding or recent glomerular lesion In view of the serious side-effects of phenacetin in certain individuals, it would seem justifiable to omit this drug from the numerous analgesic mixtures available to the general public

Summary

Of two cases of hæmolysis and acute oliguric renal failure, one followed ingestion of small amounts of phenacetin, and the other treatment with *p*-aminosalicylic acid

In each case the hæmolysis was shown to be due to the production of an autoantibody, acting on the patient's red cells in the presence of the drug

The acute tubular necrosis may have been secondary to the hæmolysis Alternatively, the renal cells may also have been damaged directly as the result of a hypersensitivity reaction

We wish to thank Prof J V Dacie and Dr M D Milne for their advice and interest in the study of these patients

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Addendum

Since this paper was written, a case-report of phenacetin-induced acute hæmolytic anæmia, associated with diminished red-blood-cell content of reduced glutathione, has been published (I B Houston and A M Barlow, *Lancet*, 1959, ii, 1062)

FREEZING-POINT OF HUMAN SKIN

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Lewis and Love (1926) reported that human skin did not freeze until it was cooled to −2 2°C, and could often be supercooled to much lower temperatures They made these estimates by pressing metal bars cooled to a known temperature on to the skin Ungley (1949) and McCance et al (1956) stated, probably on this evidence, that frostbite could not have contributed to the immersion injuries they reported in men immersed in seawater, which freezes at −1 9°C R B Lewis (1951) reported that when the legs of rabbits were plunged into a freezing mixture the deep temperature of their legs stabilised for a time at about −2 2°C, suggesting that this latter was the true freezing-point of the tissues However, Smith (1954), Lovelock and Smith (1956), and Appelboom et al (1958) reported that the true freezing-point of mammalian tissues was close to that of blood, which freezes at about −0 55°C (Margaria 1930)

It therefore seemed important to re-examine by a different technique to that of Lewis and Love (1926) the question of whether human skin can freeze at a higher temperature than −1 9°C, the freezing-point of sea water, and to attempt to measure accurately its true freezing-point

Methods

The little fingers of healthy men and women aged 18–38 were used in all "in-vivo" experiments In most cases a rubber tourniquet was applied to the base of the finger to stop the circulation, since without a tourniquet changes in blood-flow caused fluctuations in temperature which interfered with the determination of true freezing-point A thermojunction made from welded 34-gauge copper-and-constantan wire was either applied to the surface of the finger by zinc-oxide plaster, or inserted for a length of 1 cm into an intracutaneous track made previously in the deeper layers of the epidermis on the pad of the finger by a needle (Keatinge 1957) Another method attempted twice was to strap the two little fingers together, with a thermojunction between them However, the temperature between the two fingers fell so slowly that the risk of injury due to prolonged freezing of the more exposed parts of the finger made it necessary to abandon these experiments before the freezing-point could be determined On another occasion a subcutaneous needle thermocouple was used. The cold junction of the thermojunction was in a vacuum flask of distilled water and ice, and the electromotive force was led to a direct-reading galvanometer This apparatus was calibrated and was accurate to ±0 01°C

Before most experiments the entire finger, with the thermocouple and tourniquet in place, was cooled in a mixture of ice and water until the temperature of the junction had fallen to near 0 C This required 10 minutes in most cases and rather longer in others The purpose of pre-cooling was to reduce the thermal gradients in the finger at the time it was put into the brine, and thereby improve the accuracy of estimation of the true freezing-point of the skin In many cases, when several layers of plaster were applied to a finger, it was enclosed in a rubber finger-stall during pre-cooling, to prevent fresh water being absorbed by the plaster and disturbing the freezing-point determination The finger-stall was removed before the finger was put into the brine The distal phalanx only was then immersed in a freezing mixture of brine and ice This was in a circular container and was stirred mechanically so that the mixture flowed steadily past the finger The temperature of the mixture was measured by a mercury thermometer accurate to 0 01°C, and was kept at −1 9±0 02°C by adding salt when necessary

Results

Freezing of Fingers in Brine at −1 9°C

Fig 1 shows the temperature recorded from the surface of the pads of the terminal phalanges of W R K 's and P C 's little fingers in brine at −1 9°C In each case the thermojunction was covered by two strips of zinc-oxide plaster 3 mm in width, circulation to the finger had been arrested by a tourniquet, and the finger had been pre-cooled in ice and water at 0°C for 10 minutes before it was put into the brine In brine the temperatures at first fell sharply towards that of the brine, but, after 1 minute in the case of P C and 1 minute 15 seconds in the case of W R K , they rose rapidly to about −1 2°C, remained at this level for about 1 minute, and then drifted slowly downwards again Each finger was removed from the brine after 7 minutes, and at the end of this time they felt and sounded hard when tapped with a piece of wood

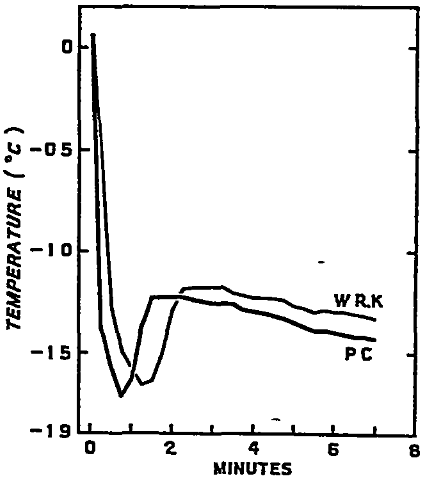

Fig 1—Surface temperatures of the little fingers of W R K and P C. in brine at −1 9 C (circulation arrested by tourniquet, thermocouple covered by two layers of plaster)

Table I shows the results of similar experiments on three other men and six women The procedure in these was identical with that in the experiments on W R K and P C except that the fingers were left in the freezing mixture for only 4 minutes in most cases In all except one case there was a sharp rise in temperature starting 45 seconds to 1 minute 45 seconds after the distal phalanx was immersed in brine, and the fingers were hard to the touch when removed In one case the temperature fell irregularly, probably due to brine reaching the thermo-

TABLE I—SURFACE TEMPERATURES OF LITTLE FINGERS DURING FREEZING IN BRINE AT −1 9 C

Subject no	Sex	Lowest temp reached (C)	Plateau temp attained (C)	Start of rise in temp (min after immersion)	Appearance of finger at conclusion	Duration of immersion in brine (min)
1	F	−1 50	−1 22	1 5	Hard, white	4
2	F	−1·43	−1 25	1 5	" "	4
3	F	−1 55	−1 21	1 25	" "	4
4	F	−1 73	−1 01	1 75	" "	4
5	M	−1 40	−1 15	1 0	" "	4
6	F	−1 86	−1 76	0 75	" "	4
7	M	−1 87	−1 53	1·0	" "	4
8	F	•	•	•	" "	7
9	M	−1 64	−1 53	1 0	" "	4
Mean		−1·62	−1 33	1 22		

• Surface temperature of this finger fell irregularly, probably owing to plaster allowing brine to reach thermojunction.

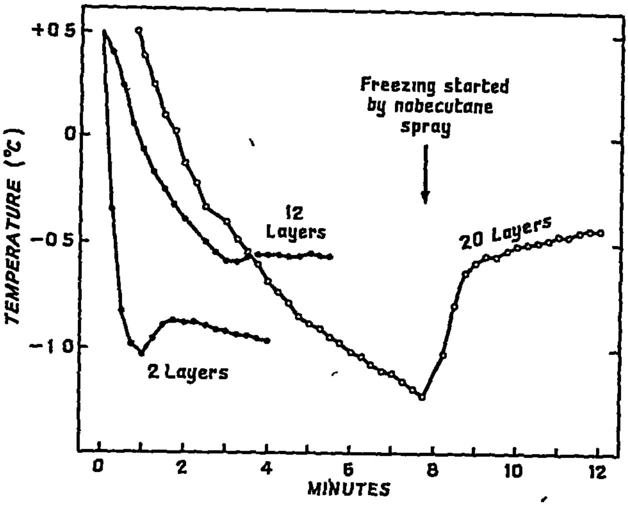

Fig 2—Temperature recorded from intracutaneous tracks in W R K 's little finger in brine at −1 9°C (circulation arrested by tourniquet, thermocouple and track covered by varying thicknesses of plaster)

junction, but this finger like the others appeared hard, white, and frozen when removed after 7 minutes The temperature in the other fingers rose to a plateau level usually at about −1 3°C

True Freezing-point of Skin

Fig 2 shows the results of three experiments on W R K which were representative of a number made on him and P C to try to determine the freezing-point of the skin more accurately The thermojunction was inserted into an intracutaneous track instead of lying on the surface, and was covered by varying thicknesses of plaster The finger was pre-cooled in ice and water to near 0°C in every case, and before the experiment with 20 layers of plaster was protected by a rubber finger-stall during pre-cooling in fresh water With 2 layers of plaster the temperature rose to −0 85°C when the finger started to freeze and then drifted downwards With 12 layers, the temperature rose to −0 55°C, only slightly higher than the level to which it had fallen, and remained steady With 20 layers of plaster, the finger did not freeze spontaneously Freezing was, however, initiated by spraying it briefly with 'Nobecutane', and its temperature rose rapidly to −0 63°C and thereafter drifted upwards more slowly

Table II shows the results of a number of experiments of this type on W R K and P C using an intracutaneous or (in one experiment) a subcutaneous thermocouple in the tip of a needle In all cases when more than 6 layers of plaster were applied they indicated a freezing-point between −0 53 and −0 65°C, the results for P C being rather lower than those for W R K Soaking of W R K 's finger in fresh water for 30 minutes had little effect on its freezing-point The subcutaneous needle thermojunction used in one experiment on W R K gave a rather lower figure, probably because of stem error

Supercooling

In all the nine experiments recorded in table I the fingers, which were previously soaked in fresh water and ice, started to freeze spontaneously within 2 minutes of immersion However, there was always a rise in temperature when freezing started, showing that there had been some supercooling

P C 's little fingers froze spontaneously in brine at −1 9°C, even when they had been protected from fresh water during pre-cooling W R K 's fingers usually froze spontaneously in brine at −1 9°C when they had been previously soaked in fresh water, but failed to do so on one occasion, and failed to freeze on all five occasions when they were immersed for 8–15 minutes in brine at −1 9°C without preliminary soaking in fresh water Rubbing a supercooled finger with wood or ice always failed to initiate freezing, but spraying a small part of the skin with nobecutane started freezing on all of the ten occasions on which this was done, presumably by lowering the surface temperature of a small area of skin briefly to a level sufficient to overcome supercooling

There was never any difficulty in telling when freezing took place Apart from the sudden rise in temperature the skin suddenly became white in appearance and hard to the touch, with a clear line of demarcation from the non-frozen tissue There was often also a sudden sharp pain when freezing was started by the spray, though this was usually absent in spontaneous freezing

Freezing with Circulation Present

P C 's little finger was dipped into brine at −1 9°C without any pre-cooling and without a tourniquet The immersed skin froze hard after 4 minutes

Injury

The subjects whose fingers were frozen on a single occasion for up to 4 (or, in one case, 7) minutes experienced severe pain during rewarming, but the fingers looked normal and felt virtually normal the next day, and none subsequently became blistered However, the day after the distal phalanx of W R. K 's right little finger was frozen for the fourth time, it became considerably

TABLE II—DETERMINATION OF THE FREEZING-POINT OF SKIN

Subject	Site of thermojunction	Layers of plaster over thermojunction	Whether finger was protected from fresh water during pre-cooling	Start of freezing (min)	Temperature at onset of freezing (C)	Temperature after freezing (C)
P C	Intracutaneous	6	No	Spontaneous 2 5	−1 35	−0 65
	"	12	No	2 25	−0 75	−0 60
	"	15	Yes	" 4 5	−1 40	−0 62
	"	20	Yes	" 2 5	−0 94	−0 64
	Mean				−1 11	−0·63
W R K	Shallow subcutaneous	0	No	Spontaneous 2 0	−1·50	−0 81
	Intracutaneous	2	No	1 25	−1 03	−0 87
	"	6	No	" 3 25	−0 84	−0 59
	"	12	No	" 3 5	−0 59	−0 55
	"	10	Yes	Spray 2 75	−0 68	−0 60
	"	10	Yes	" 2 5	−0 80	−0 56
	"	10	Yes *	" 2 5	−0 84	−0·53
	"	20	Yes	" 7 75	−1 22	−0 63
	Mean (only experiments with 6 or more layers of plaster included)				−0 83	−0 58

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* Finger soaked for 30 minutes in distilled water, then mopped dry, before thermojunction was inserted in track and plaster applied Procedure and track were otherwise identical with the previous experiment

painful and hyperæmic (fig. 3). The hyperæmia and tenderness subsided during the next 4–5 days, but during the next 2 weeks most of the skin on it blistered off. Lesser degrees of hyperæmia and blistering were observed after repeated freezing of W. R. K.'s left little finger and P. C.'s little fingers. The more severe degrees of hyperæmia and tenderness were produced only when a finger was frozen at a time when it was still slightly tender as a result of an earlier freeze, although the fingers were not frozen more often than once a day, or for more than 8 minutes at a time.

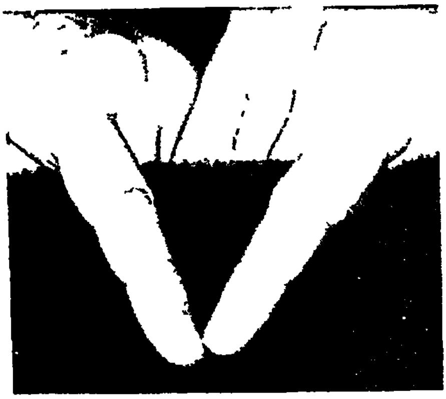

Fig. 3—Appearance of W. R. K.'s right little finger after repeated short periods of freezing in brine at −1·9°C.

To determine whether the damage was really a result of freezing, or whether it was a result of low temperature per se, an additional experiment was performed on W. R. K. and subject 7.

The terminal phalanx of the left little finger of each of them was supercooled in brine at −1·9°C, with circulation arrested, for 15 minutes, and in each case was still soft at the end of the experiment. On the same day the right little finger of each was also cooled in brine for 15 minutes, the procedure being identical except that, after $3^1/_2$ minutes in the brine, freezing was started by a nobecutane spray. The finger froze immediately, and at the end of the experiment, 11 minutes later, felt very hard. Neither of subject 7's or W. R. K.'s little fingers had been frozen in the 3 weeks before this experiment. The fingers were rewarmed by running water at 15°C over them at the end of the experiment, and care was taken not to subject them to trauma until they had been rewarmed.

The next day the fingers which had been supercooled looked and felt normal, while the fingers which had been frozen were tender and red and their skin temperatures were 4–8°C higher than those which had been supercooled. The tenderness and difference in skin temperature decreased and had virtually disappeared 5 days later.

Discussion

These results show that, contrary to general belief, human tissues can freeze at the temperature of freezing sea-water and that they can sustain injury as a result of being frozen at this temperature.

Lewis and Love (1926) were unable to freeze human skin by placing it in contact with metal at temperatures above −2·2°C, and Lewis (1941) stated that "freezing of feet while immersed in sea water can hardly occur for the temperature of the water cannot fall below −1·9°C, its own freezing point." This apparent discrepancy with the present findings is probably due to the difference in method, large temperature gradients must exist in the skin when a metal bar is pressed on the skin of a warm limb, and even the most superficial part of the skin must be at a higher temperature than the bar. Lewis and Love (1926) observed that supercooling of skin was common and could be reduced by soaking the skin in fresh water. The present experiments confirm this, dry fingers sometimes supercooled and sometimes froze in brine at −1·9°C, but they almost always froze when they had been soaked in fresh water beforehand. They failed to do so on only one occasion after such preliminary immersion.

In the experiments with surface thermocouples covered by two layers of plaster their temperature rose to −1–−1·76°C when the skin froze. Since the thermocouples were between the skin and the brine, the temperature they recorded must have been below that of the skin, and the true freezing point must have been higher. The experiments using intracutaneous tracks and 6–12 layers of plaster, on the other hand (table II, fig. 2) gave stable temperatures for some minutes in the region −0·6°C when freezing started. When more layers of plaster were applied the temperature failed to stabilise after the sudden rise when freezing started, and continued to drift upwards, probably because the junction lay in a region between the freezing tissue and the warm, non-immersed part of the finger. The position of the breaks in these curves also, however, indicates a true freezing-point of about −0·6°C.

No previous determination of the true freezing-point of human skin appears to have been made, Lewis and Love (1926) were clear that their method determined the temperature at which supercooling was overcome rather than the true freezing-point, which must be higher. The freezing-point of mammalian tissues has been reported to be −2·2°C (R. B. Lewis 1951), but Lovelock and Smith (1956) and Appelboom et al. (1958) have found it to be about −0·56°C. This is approximately the freezing-point of blood, which may vary from −0·51 to 0·61°C with varying degrees of hydration of the body (Margaria 1930). It is a familiar observation that human skin becomes wrinkled when soaked in fresh water, and must therefore absorb water which will raise its freezing-point somewhat. Such absorption of water by the surface layers may reduce the power of skin to supercool (Lewis and Love 1926, table II), but since only a trivial elevation of freezing-point, within the limit of experimental error, could be obtained by soaking for 25 minutes (table II), the freezing-point at least of the deeper layers of the skin cannot have been greatly altered by these means.

It might be argued that cold vasodilatation should normally protect the extremities from freezing in brine at −1·9°C. However, although cold vasodilatation always appears eventually in the fingers of even chilled men when the fingers are cooled to 0°C, the dilatation always takes several minutes, and often 30 minutes or more, to start (Keatinge 1957). The extremities can clearly freeze solid long before this time, and freezing of P. C.'s little finger was observed 4 minutes after immersion in brine at −1·9°C even without previous cooling and with the circulation intact.

Although freezing at −1·9°C for periods of 4–7 minutes did not give rise to any significant after-effects, freezing for $11^1/_2$ minutes caused pain and hyperæmia for several days. Repeated freezing for shorter periods at intervals of a day or two caused pain, hyperæmia, and blistering of the skin. Lewis and Love (1926) reported that freezing of human skin caused more injury than supercooling, but Smith (1954) reported that supercooling, as well as freezing, could cause necrosis of the extremities of hamsters Since supercooling of fingers in these experiments did not cause the after-effects produced by freezing them at the same temperature and for the same time, and since on previous occasions fingers have been kept at 0°C for much longer without injury (Keatinge 1957), the change observed in these fingers must have been due to freezing The results obtained by Smith (1954) in hamsters suggest that the injury would have been greatly increased if the tissue had been subjected to trauma while frozen, trauma to frozen fingers was carefully avoided in the present experiments

The greater injury caused by repeated freezing in these experiments contrasts with the report of Fuhrman (1957) that a brief freeze of the legs of rats (1 second at −25°C) decreased the damage caused by subsequent freezing 2 days later The difference in the duration and temperature of freezing in this worker's experiments, and the fact that rats were used, may account for the apparent contrast with the present results

The freezing-point of sea-water in the Arctic Ocean is variable, particularly near the mouths of Arctic rivers, but in the region of the Norwegian sea, as in most of the ocean, it is about −1 9°C (Sverdrup et al 1942) Many immersion injuries were suffered by men in ships sunk in this area in the late war (Ungley 1949, McCance et al 1956) The present results show that frostbite may contribute to such injuries and is particularly likely if the skin is wet before immersion It is clearly important to provide sufficient protection to keep the skin temperature 1°C or more above water-temperature when immersion in freezing sea-water is unavoidable

Summary

Human fingers cooled to −1 9°C, the freezing-point of sea-water, usually froze They almost invariably did so when they had been soaked in fresh water and ice beforehand

The true freezing-point of human fingers was found to be between −0 53 and −0 65°C

Freezing in brine at −1 9°C for 4–7 minutes, without trauma in the frozen state, caused no significant injury However, freezing for $11^{1}/_{2}$ minutes or repeated freezing for shorter periods caused hyperæmia and tenderness lasting several days and, in the case of repeated freezing, blistering of the skin No ill-effects were produced by supercooling fingers to the same temperature for the same time

Earlier statements that human tissues cannot freeze in sea-water appear to have been based on indirect evidence

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FÆCAL LOSS OF FLUID, ELECTROLYTES, AND NITROGEN IN COLITIS BEFORE AND AFTER ILEOSTOMY

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A WELL-RECOGNISED danger of ulcerative colitis is considerable depletion of fluid and electrolytes from excessive gastrointestinal loss This may arise either because of severe diarrhœa in the intact patient undergoing medical treatment, or because of profuse postoperative discharge from the ileostomy The magnitude of the loss in each of these circumstances has been specially studied by Lubran and McAllen (1951) and Crawford and Brooke (1957) These workers have stressed particularly the risk of potassium deficiency in the medically treated colitis patient who still has a functioning large intestine, and of sodium depletion after an ileostomy has been established The investigations which we here report were undertaken as an amplification of this previous work, but our findings, though largely confirmatory, differ in certain important respects

Material and Methods

Fæcal loss of fluid, sodium, potassium, and, in certain circumstances, nitrogen was estimated in nine patients awaiting operation for ulcerative colitis, and in sixteen patients after operation, which in all cases took the form of a one-stage ileostomy with total proctocolectomy Similar investigations were made in two cases with ileostomies established for 12 months Three of the preoperative patients and the two patients with established ileostomies were given an ordinary ward diet, but six had extensive balance studies, being given various quantities of sodium and potassium with a fixed intake of 3000 ml water daily

In most of the postoperative cases the fluid and electrolytes given accorded with the needs of ordinary postoperative management Intravenous infusion was continued as a rule for only 24–36 hours Fluids were given by mouth immediately after operation, and were gradually increased in amount from 30 ml hourly until, by the 4th or 5th postoperative day, a light diet was taken, and by the 8th–12th days the diet was fairly full In three patients, however, a fixed intake of 3000 ml of fluid daily, together with sodium 300 mEq and potassium 87 mEq , was maintained throughout the period of investigation—i e , up to the 12th postoperative day

Of the sixteen patients studied after operation all except one recovered without complicaton Six had steroid therapy during and after operation (dosage 100 mg t d s for 2 days, 100 mg b d for 2 days, and then reduction of the total dose by 50 mg. daily to a maintenance dose of 50 mg daily, which was continued until the end of the study period) Of these six patients, five recovered uneventfully, but in one peritonitis necessitated further operation to drain the abdomen After this she progressed satisfactorily, although profuse ileostomy diarrhœa was associated with the intraperitoneal sepsis

Collection of Specimens and Chemical Analysis

24-hour collections of urine and fæces or ileostomy fluid were made Each specimen was measured for volume, and analysed for sodium, potassium, and nitrogen content

Volume of fæces or ileostomy fluid—The specimen was transferred to a graduated volumetric flask, using a weighed amount of water, and filled to the mark with a weighed amount of water (Thus volume of specimen = volume of flask – weight of water added) The contents of the flask were then homogenised If frothing appeared, a few drops of caprylic alcohol were added

Sodium and potassium estimations—To 10 ml of the homogenised "fluid" in a conical flask concentrated nitric acid 2 ml (analytical reagent) was added (The acid had previously been freed from all lower oxides of nitrogen by boiling with $^1/_4$ of its volume of water until the brown discoloration disappeared) With a glass bubble in the top of the flask, the mixture was brought to the boil for a minute or two After cooling, the digest was transferred to a 50 ml graduated flask The volume was made up to the mark with distilled water, and the contents were mixed thoroughly The mixture was filtered, and the filtrate was diluted similarly with water The sodium and potassium contents were measured in an 'Eel' flame-photometer

Nitrogen estimation—The macro-Kjeldahl method was used 10 ml of homogenised fæces or ileostomy fluid or 5 ml of urine was digested with concentrated sulphuric acid 20 ml and copper sulphate 0·2 g in a 250 ml Kjeldahl flask Heating was continued for 1 hour after the colour had cleared After cooling, distilled water 80 ml was added, followed by caustic soda 40% in excess (phenolphthalein indicator) The ammonia was distilled over into 0 2 N sulphuric acid 20 ml, containing methyl-red as indicator When the volume of the liquid in the Kjeldahl flask had been reduced by half, distillation was discontinued The excess acid in the receiving flask was titrated with 0 1 N sodium hydroxide, and the nitrogen content was then estimated

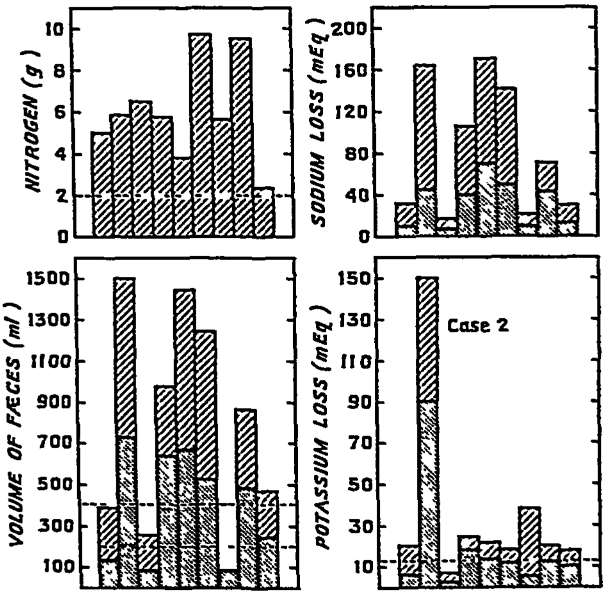

Fig 1—Daily minimum and maximum fæcal volumes and sodium, potassium, and nitrogen loss in nine colitis patients before operation

Results

BEFORE OPERATION

Volume of fæces—Fig 1 shows the minimum and maximum fæcal volumes in the nine patients investigated before operation The normal maximal fæcal volume of 400 ml was exceeded in all except two In three patients the fluid intake was increased from 1500 ml to 3000 ml per day, without increase in fæcal volume But when the fluid and sodium intakes were increased simultaneously the fæcal volume rose rapidly

Sodium excretion—Accepting the normal fæcal loss of sodium as 2–5 mEq per day, the results in all the patients studied (fig 1) show that the excretion was greatly in excess of normal Although the sodium loss varied between 9 and 170 mEq per day, in no patient was this sufficient to produce the clinical syndrome of sodium depletion In six patients (cases 4–9), in whom the fluid intake was 3000 ml daily, the sodium intake was known The table shows the effect of a higher sodium intake (cases 7–9) on the fæcal and urinary volumes and the fæcal and urinary excretion of sodium (These data were compiled after an initial period of 6 days for equilibration) When increased quantities of sodium were taken by mouth both the sodium content and volume of the fæces increased, this may indicate a defective absorptive capacity of the large bowel for sodium In seven of the nine patients investigated the sodium excretion was proportional to the fæcal volume (fig 2) Though the sodium content of the fæces was remarkably constant in any one patient despite considerable fluctuations in volume, the amount of sodium varied from patient to patient

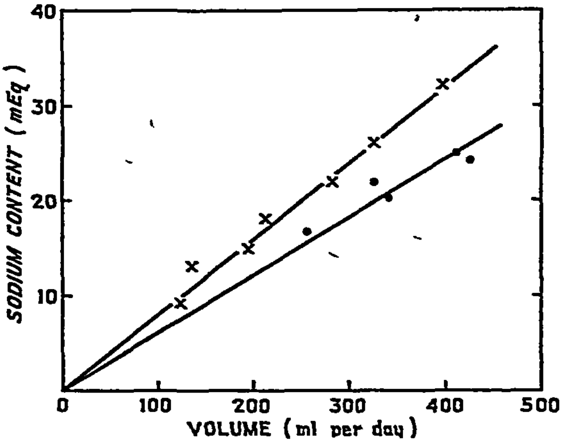

Fig 2—Sodium loss in two of the seven patients in whom sodium excretion was proportional to fæcal volume

Potassium excretion—As fig 1 shows, the loss of potassium exceeded the normally accepted value of 6–12 mEq per day in all except one patient With this exception the potassium loss was relatively little, being only 2–3 times the average daily normal In this patient (case 2, column 2) the loss of potassium varied between 90 and 167 mEq per day, but despite this (and without potassium supplements by mouth) the serum-potassium level remained within normal limits In five patients the

SODIUM EXCRETION IN COLITIS PATIENTS ON LOW AND HIGH SODIUM INTAKE

—	Case no					
	4	5	6	7	8	9
Daily intake of sodium (mEq)						
Day 1	103	92	110	237	277	334
„ 2	103	92	110	237	277	334
„ 3	103	92	110	237	277	334
„ 4	103	92	110	237	277	334
„ 5	103	92	110	237	277	334
6	103	92	110	237	277	334
Daily fæcal excretion of sodium (mEq)						
Day 1	18	66	23	49	71	95
„ 2	15	60	25	83	70	65
„ 3	14	57	25	108	90	99
„ 4	9	53	20	114	40	120
„ 5	9	60	16	123	108	148
„ 6	18	52	24	144		170
Fæcal volume (ml)						
Day 1	488	825	319	515	781	870
2	89	676	411	662	830	692
„ 3	312	624	426	1092	895	920
„ 4	232	590	338	1072	619	1030
„ 5	181	693	251	1000	940	1359
„ 6	306	604	481	1225		1472
Daily urinary sodium (mEq)						
Day 1	91	4	56	202	175	209
„ 2	69	7	86		164	248
„ 3	114	10	88	157	172	148
„ 4	91	13	82	116	172	150
„ 5	97	16	80	59	105	84
„ 6	99	17	72	61	206	103
Daily urinary volume (ml)						
Day 1	2014	635	1106	920	1200	1900
„ 2	1850	1220	1600		850	1430
„ 3	2050	1100	1470	860	1400	1250
„ 4	2035	1110	1670	700	955	1220
„ 5	2048	720	1770	580	845	878
„ 6	2280	1350	1470	640	1270	1300

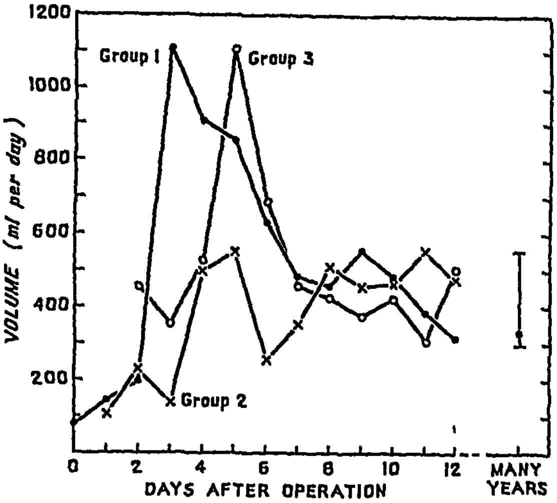

Fig 3—Volume of ileostomy discharge in the 3 groups of patients not treated with steroids

fæcal potassium loss was related directly to volume, but, as with the sodium loss, this was not applicable to the group as a whole, neither did potassium loss and fæcal volume necessarily correlate in those patients in whom sodium loss correlated with the volume of fluid excreted

Nitrogen excretion—In seven patients in whom the fæcal nitrogen loss was studied, the normal value of 2 g per day was exceeded This caused the fæcal nitrogen loss to fluctuate between 20% and 30% of the daily intake of protein, compared with the normal of 10% Four of the six patients subjected to balance studies (daily nitrogen intake 9 4–12 g) were in negative balance—a result in keeping with their progressive weight loss

AFTER OPERATION

Uncomplicated Cases not having Steroids

The eleven patients have been divided into 3 groups depending on the time of onset of ileostomy discharge after operation In group 1 (two patients) the discharge started on the day of operation, in group 2 (four patients) it began on the 1st day after operation, and in group 3 (five patients) it was delayed until the 2nd day

Volume of ileostomy discharge—The average volume of ileostomy discharge in the 3 groups is shown in fig 3

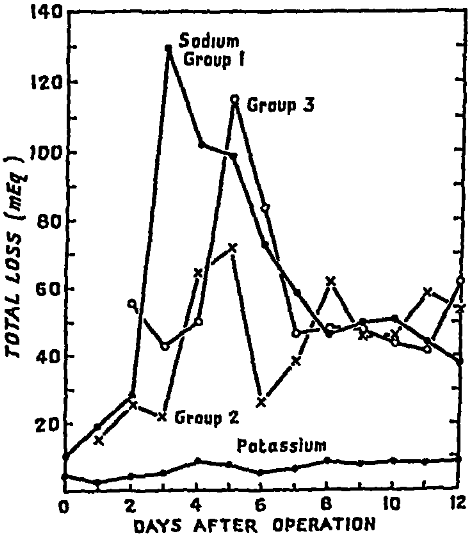

Fig 4—Average total sodium and potassium loss after operation in the patients not treated with steroids

After the ileostomy began to function the volume of discharge increased rapidly until, between the 3rd and 5th days, a maximum was reached The volume then diminished until, by the end of the 1st week, the volumes excreted were within the range of the established ileostomy —i e , between 200 and 500 ml per day After the period of greatest excretion the consistence of the ileostomy discharge rapidly changed until, by the end of the first 10 days, it was porridge-like, resembling the fæces from a long-established ileostomy In only two patients was the volume of discharge more than 2000 ml per day, and this abnormal amount was passed once only in each case

Sodium—The daily average sodium excretion via the ileostomy was calculated for each of the 3 groups The total loss of sodium did not exceed 130 mEq per day in any patient, and the greatest loss of sodium corresponded to the greatest discharge from the ileostomy In all patients within 1 week of operation the daily sodium loss fell to 40–60 mEq , a rate of excretion such as is found with long-established ileostomy Fig 4 shows the average daily loss of sodium for each group Comparison with fig 3 suggests that sodium and fluid loss are closely related, indeed these two factors are directly proportional, as is shown in fig 5, calculation of their correlation coefficient exceeding the 0 1% level of significance Thus the sodium content of the ileostomy fluid seemed to remain constant at 120 mEq per litre when volumes within the normally accepted range were excreted

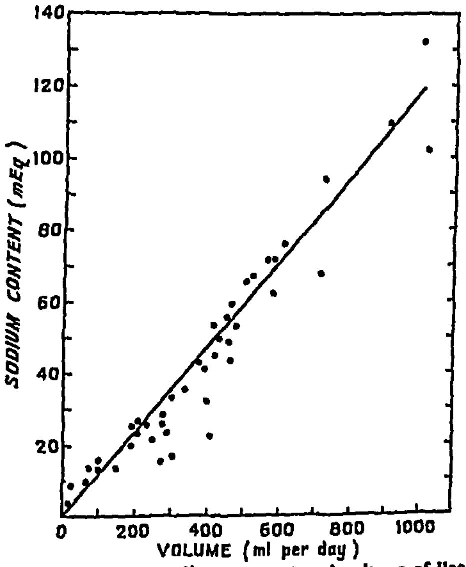

Fig 5—Relation between sodium content and volume of ileostomy fluid in patients not treated with steroids

Potassium—The total potassium loss varied between 1 and 12 mEq daily But whereas the correlation between sodium content and fluid excreted satisfies all statistical inquiry, this was not true of potassium, the loss of which varied from day to day within very narrow limits

Nitrogen—Nitrogen excretion from the ileostomy was negligible in the seven patients in whom it was measured The amount varied between 0 4 and 1 8 g daily, these values representing the minimum and maximum values over a period of 15 days' observation The loss of nitrogen is thus not important in the practical management of ileostomy patients

Cases treated with Cortisone

The following data relate only to the postoperative period Cortisone seemed to exert an influence on both

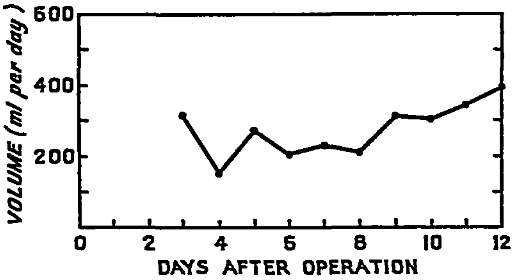

Fig 6—Average volume of ileostomy discharge in five cortisone-treated patients

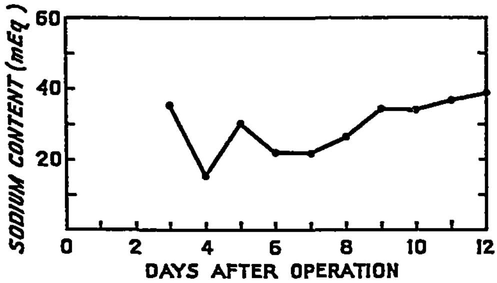

Fig 7—Average total daily sodium loss in five cortisone-treated patients.

the quantity of the ileostomy discharge and the concentration of its constituents

Volume—The time-interval between operation and the onset of ileostomy function was uniformly delayed until the 3rd postoperative day in patients treated with cortisone Fig 6 shows that, whilst the volume of the ileostomy discharge ultimately reached that typical of the patients who did not have steroids, no peak of excretion appeared in the early postoperative period

Sodium excretion—The total daily sodium excretion in the five patients investigated is shown in fig 7 The greatest total loss of sodium in a single case in this group was 87 mEq per day, but in the whole group, in which 100 observations were made, only 10 values exceeded 50 mEq per day As with fluid excretion there was no peak of sodium excretion The sodium content of the discharge was 109 mEq per litre as compared with 120 mEq per litre in the patients not treated with steroids—a statistically significant difference.

Potassium—The total potassium loss via the ileostomy varied between 3 and 9 mEq per day, these values being similar to those observed in the cases not treated with cortisone The total potassium loss increased with the volume of the discharge and then remained relatively constant

Nitrogen—Loss of nitrogen from the ileostomy was specifically investigated in one patient only, but, since values between 0 5 and 1 7 g per day were found, the loss of nitrogen is probably similar to that previously observed in the patients not treated with steroids

Ileal Dysfunction Associated with Peritonitis in a Patient having Steroids

In one patient ileal dysfunction was apparently due to intra-abdominal sepsis When the abdomen was re-explored on the 4th postoperative day general peritonitis was found, and the abdomen was drained, after a difficult convalescence the patient recovered The total fluid, sodium, and potassium loss in this case are recorded in fig 8 This shows the greatly increased volume of fluid excreted throughout the period of observation, and the high loss of sodium and potassium amounting to as much as 300 mEq of sodium and 60 mEq of potassium daily Whilst the sodium content fell below the normal of 120 mEq per litre, the potassium content was abnormally high In such circumstances there is danger of both sodium and potassium depletion, and intravenous supplements of these cations were required throughout the period of investigation

The changes in the ileostomy discharge in this case seem to us characteristic Indeed another patient in whom peritonitis developed on the 18th postoperative day had similar changes in the ileostomy discharge, although the chemical data were insufficient for us to report this case in detail

Discharge from the Long-established Ileostomy

In two patients whose ileostomy discharge was investigated some time after the fistula was established the results agree with those already described during the 2nd week of function in patients not having steroids

In both our patients the total daily volume of discharge fluctuated between 300 and 500 ml The sodium content agreed closely with the previous findings, being 120 mEq per litre. The potassium loss ranged from 3 to 4 8 mEq per day, and even in the same patient the content varied

The nitrogen loss differed little between the patients with recently established and long-established ileostomies, values between 0 5 and 2 g daily being observed in the latter

Discussion

The Preoperative Patient

Contrary to the reports of Gardner et al (1949) and Lubran and McAllen (1951) potassium deficiency was not a problem in the preoperative management of the seven patients we studied in detail (neither was lack of potassium a notable feature in ninety-eight additional cases which came under our care for surgical treatment during the past 4½ years, being evident in only two of these patients) This is perhaps surprising in view of the earlier findings of potassium depletion in four out of thirty consecutive cases of colitis observed by Lubran and McAllen (1951) But in our cases the fæcal volumes were relatively small, never being greater than 1500 ml per day, whereas

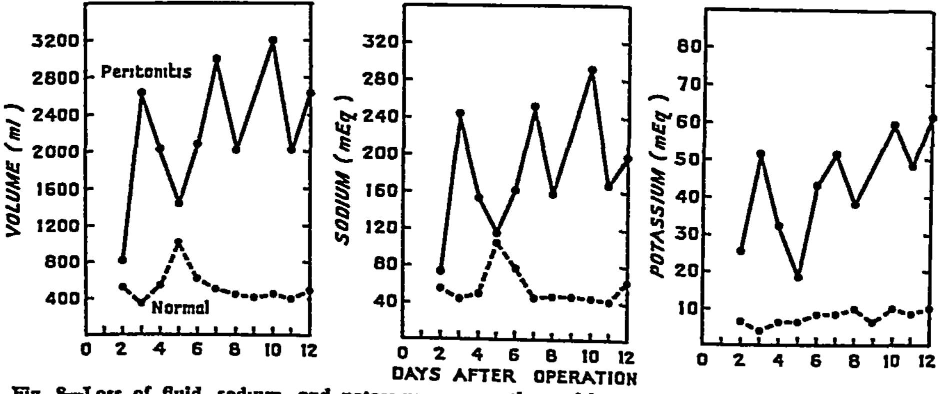

Fig 8—Loss of fluid, sodium, and potassium in a patient with gross intraperitoneal inflammation compared with the "normal"

in Lubran and McAllen's patients the daily loss of fluid per rectum was as much as 2500 ml Welch et al (1937) and Lubran and McAllen (1951) found that electrolyte loss was determined by the fæcal volume Welch et al found that the sodium and potassium loss in colitis patients was (jointly) equivalent to a 70% isotonic solution, Lubran and McAllen thought the fæcal fluid was isotonic with plasma

Our findings suggest that the cation equivalent of the fæces varies, ranging from hypotonic to isotonic in different patients and from day to day, depending on fæcal bulk Lubran and McAllen (1951) found that the loss of sodium and potassium was directly proportional to the volume of fluid excreted But in our experience, though the loss of cations may be proportional to the volume, the observations in one patient are not applicable to the next, neither is a proportional potassium loss necessarily found in patients with a fixed relation for sodium

Our findings suggest also that in colitis the inflamed colon is unable to absorb sodium, for when increased amounts of sodium were given by mouth increased quantities were lost in the stools, which were of greater volume

In general the loss of nitrogen in the colitis patient is higher than normal, as shown by the increased fæcal loss The greatest fæcal loss of nitrogen in any of the seven preoperative patients we studied was 10 g per day (roughly equivalent to 60 g of protein), exceeding greatly the normal of 2 g per day Miller et al (1949) alleged that a fæcal loss of up to 100 g of protein daily might arise in severe cases of colitis, and therefore favoured primary colectomy instead of simple ileostomy, leaving the colon intact Whilst we cannot confirm their estimations, we think that a sustained daily loss of 60 g of protein could be seriously detrimental, particularly postoperatively, when intake might be much reduced

The Ileostomy Patient

Our findings regarding sodium excretion from the recently formed ileostomy are notably at variance with those of Crawford and Brooke (1957) These workers claimed that immediately after the establishment of an ileostomy the fæcal sodium content was at first very high, amounting to 200–400 mEq per litre, and that as the fæces gradually thickened the sodium content fell to the same level as is found in patients with long-established ileostomies—namely, about 150 mEq per litre But if this initial value were added to the potassium loss of 10 mEq per litre which they found, a hypertonic fluid would be excreted via the recently established ileostomy This would be somewhat remarkable Apart from conflicting with our findings, it conflicts also with the findings of Lans et al (1952), who estimated, by aspirating the ileal contents through nasal or oral tubes, that the sodium content was about 121 mEq per litre (range 88–146 mEq) and the potassium content 9 6 mEq per litre (range 4 8–13 6 mEq), which implies that the ileostomy discharge should be isotonic or slightly hypotonic relative to plasma

Crawford and Brooke (1958) admitted later that the high sodium content they had found in the ileostomy fluid immediately after operation was difficult to understand After a careful check on their methods they suggested a possible explanation All their patients were given sodium-chloride tablets by mouth after operation, and some of these might not have dissolved completely in the alimentary tract, thus being passed semidigested and dissolving later in the storage cans, thereby raising the sodium content

We found that in most patients ileostomy function began on the 2nd day after operation, that the greatest fæcal volume was excreted during the 1st week, and that the volume of discharge was then in most cases equivalent to the accepted normal for the established stoma The maximum volume was seldom greater than 1000 ml per day in the absence of complications, and we believe that if greater volumes than this are excreted the ileostomy is malfunctioning, either because of mechanical difficulties, such as obstruction, or because of inflammatory changes close to the bowel, as in peritonitis

In all our patients the sodium loss seemed to be directly proportional to the volume excreted, and in the average ileostomy patient *the sodium content was 120 mEq per litre regardless of the fæcal volume* Thus for practical purposes there is no difference in the concentration of sodium between the recent and long-established ileostomy Whilst sodium loss was directly related to the volume of ileostomy fluid, the loss of potassium varied between different patients and in the same patient from day to day, but under normal circumstances it never exceeded 11 mEq per day, which is considerably less than the normal daily intake of 50–200 mEq potassium (Thompson and King 1957) Thus in the ordinary patient after ileostomy the sodium and potassium loss is not a serious hazard, the volumes excreted are normally small, and the cation contents are together equivalent to a fluid isotonic as compared with plasma

In the practical management of uncomplicated cases the potassium loss may be ignored completely, and the sodium and fluid loss can be replaced accurately by normal saline (156 mEq of sodium per litre) intravenously in amounts equal to the volume of ileostomy fluid excreted But when some condition causes massive increase in the ileostomy discharge, the loss of water, sodium, and potassium may become critical In our case in which ileal dysfunction was due to peritonitis, the volume of fluid was sometimes as high as 3 litres per day, and never less than 2 litres per day for 14 days during the recovery period Associated with the high fluid output the total loss of sodium and potassium was considerable—between 260 and 300 mEq per day for sodium and between 20 and 60 mEq per day for potassium This single case suggests that the small intestine makes some attempt to conserve sodium, for when there was profuse ileostomy diarrhœa the fæcal sodium content was reduced to 110 mEq per litre compared with the normal of 120 mEq per litre in uncomplicated cases

The Effect of Cortisone

Many patients with ulcerative colitis have had steroid therapy before surgery, and they therefore need it during and after operation to guard against adrenal failure Such hormone administration affects the ileostomy discharge.

In 1958 Brooke reported the effect of cortisone on the ileostomy in three patients who had had this drug before and immediately after the stoma was established He found that cortisone reduced the volume of fluid excreted via both the kidney and the stoma, that the sodium content was lowered, and that the potassium content was raised In general these findings are confirmed by our present study, the sodium/potassium ratio of the ileostomy fluid (normally 11–18 in patients with a recent ileostomy) being 6 in the cortisone-treated patients This reduction is due to diminution of the sodium content and increase of the potassium content of the fæces That this is not due to chance is shown by the effect of cortisone given temporarily to a patient with an adrenal crisis (fig 9), in this case the sodium/potassium ratio fell from 16 to 2 after cortisone was given, and rose rapidly again when cortisone was discontinued

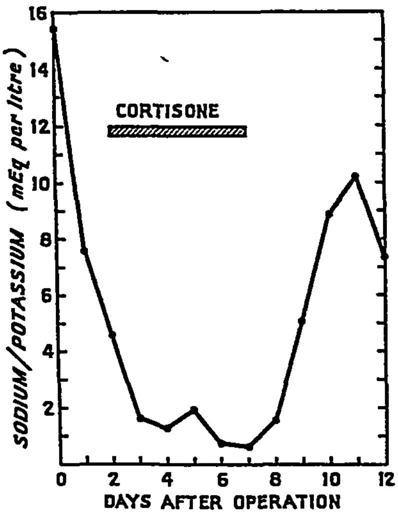

Fig 9—Effect of cortisone on the sodium/potassium ratio of the ileostomy discharge in a patient with adrenal failure

Like Brooke (1958) we found that, in general, the volume of ileostomy fluid is lowered in the cortisone-treated patient Brooke suggested that cortisone might be tried in those patients who normally have a watery ileostomy discharge in the absence of mechanical disturbances of the stoma But in the one patient we studied with this state of affairs, the volume of the ileostomy fluid did not decrease significantly over a period of 14 days' cortisone therapy Thus steroids are not always effective in checking such excessive ileostomy action

Summary

The fluid, electrolyte, and nitrogen loss was studied in nine patients with ulcerative colitis before operation and in sixteen patients after operation

Before operation the fæcal loss in all patients exceeded the normal, although the loss of potassium was not as high as was expected from the results of previous investigations

After operation the greatest excretory activity when the volume of discharge rose to as much as 1500 ml was during the 1st week The sodium content of the discharge was 120 mEq per litre, but the potassium content varied Nitrogen loss varied between 0 4 and 1 8 g daily

In patients treated with cortisone postoperatively the volume of the discharge gradually increased to normal values, without a peak The sodium content was 109 mEq per litre, and relatively large amounts of potassium were excreted

In a patient with peritonitis the loss both of fluid and cations was increased considerably, necessitating continuous intravenous supplements throughout the period studied

We wish to acknowledge with thanks a helpful exchange of ideas with Dr N F Coghill, Dr M. Lubran, and Mr B N Brooke before we started this study We are also much indebted to Miss F E Briggs, B.SC , dietitian, and to Sister Margaret Thwaites, Sister E L Moxon, and Sister Joan Womersley and their nurses for much assistance with this investigation

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ARTERIAL PERFUSION IN THE LOWER LIMB AS AN AID TO VASCULAR SURGERY

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The value of restorative procedures in the treatment of obstructive disease of the aortic bifurcation and iliac, femoral, and popliteal arteries is well established These procedures may take the form of restoring the arterial lumen (disobliteration) or a bypass of the obstruction with arterial homografts or synthetic tubes

Selection of Patients for Restorative Surgery

There are two main groups of patients (*a*) those in whom loss of the limb is inevitable in the immediate future, because of gangrene or intolerable rest pain, and (*b*) those in whom the clinical features, claudication, or ulceration are not so clamant, who can carry on even if only with reduced activity This second group includes some who find restriction of activity intolerable or impossible owing to financial or business reasons, and who should, for the purpose of treatment, be classed with group (*a*)

When assessing each patient for the advisability of restorative surgery the morbidity, mortality, and likely success of the operation must be balanced against the degree of local disability and the general state of the patient. For patients in group (*a*) there is nothing to be lost by an attempt at some restorative procedure, whereas in group (*b*) the problem is more difficult, for gangrene may be precipitated by an unsuccessful operation When advising patients in this group the position must be put to them squarely without minimising the risks Cardiac, cerebral, or other disease in an acute phase contraindicates any lengthy operation involving a certain amount of hæmorrhage A past history of coronary thrombosis is not necessarily a contraindication, though ironically enough a successful operation in a patient with valvular heart-disease may precipitate cardiac failure by reason of the increased cardiac output required

Arteriography as an aid to diagnosis and selection is indispensable without it the surgical alternatives are sympathectomy (so capricious in its effects) and amputation Arteriography reveals the precise site and extent of any arterial obstruction, whether the lesion is multiple, the degree of the collateral circulation, and the patency of the smaller vessels in the lower leg and foot Restorative operations are only suited to those cases where the principal cause for the ischæmia is in the main vessels and where the distal part of the popliteal artery is sufficiently patent to enable a satisfactory anastomosis of a bypass graft to be effected In most cases similar disease is present in the smaller vessels, and in some the poor filling of arteries with the contrast medium ('Hypaque') below the knee may be such as to discourage an attack on the main vessel Table I shows how 44 patients seen in a period of six months were assessed after arteriography

Measures to Avert Failure in Grafting

In the operative and immediate postoperative period an artery graft will fail if the blood within it clots Such clotting is the result of poor linear flow Assuming that the

TABLE I—ANALYSIS OF TREATMENT OF 44 PATIENTS ADMITTED WITH PERIPHERAL VASCULAR DISEASE OF THE LEGS OVER A SIX-MONTH PERIOD

	No
Operations	
Amputation	7
Disobliteration	6
Graft	7
Sympathectomy	3
Other	2
No restorative operation attempted	
Suitable for restorative procedure but risks unjustifiable "too good" for restorative procedure	13
Local arterial disease too extensive or systemic disease prohibitive "too bad" for restorative procedure	8

anastomosis (end-to-side) between each end of the graft and patient's artery is technically satisfactory and therefore fully patent, the cause of failure is to be looked for in the blood-flow in the femoral artery above and the popliteal artery below

1 If there is narrowing of the femoral artery or yet another obstruction above, the impelling force or head of pressure of blood entering the graft is insufficient. Because of this danger it has become the practice over the past three years to join the upper end of the graft to the common femoral or external iliac artery, and *not* to the femoral artery below the origin of the profunda femoris Thus much longer lengths of graft material (homografts) are being used than before in femoropopliteal obstructions The head of pressure may be further reduced by operative and postoperative hypotension, measures against which include adequate blood replacement. By opening up collateral channels, sympathectomy will also rob the graft of its blood-flow

2 Below the distal anastomosis there must be sufficient lumen in the popliteal artery and its branches to admit and pass on towards the foot the full flow of blood from the graft. As evidence of this we have come to rely upon a good "bleed-back" when the popliteal artery is opened But failure can still occur because, as arteriography often shows, the patency of the posterior and anterior tibial arteries is imperfect. Also any lumen is further reduced by clotting during the period of limb ischæmia that is necessary while the graft is being sewn into position Prolonged ischæmia causes muscle damage and œdema, and this in turn will obstruct small or partially blocked vessels Heparin can be administered systemically, but usually it is injected locally as heparin saline down the popliteal artery during grafting Owing to difficult situations caused by hæmorrhage and hæmatoma formation, systemic anticoagulation is not continued after the operation

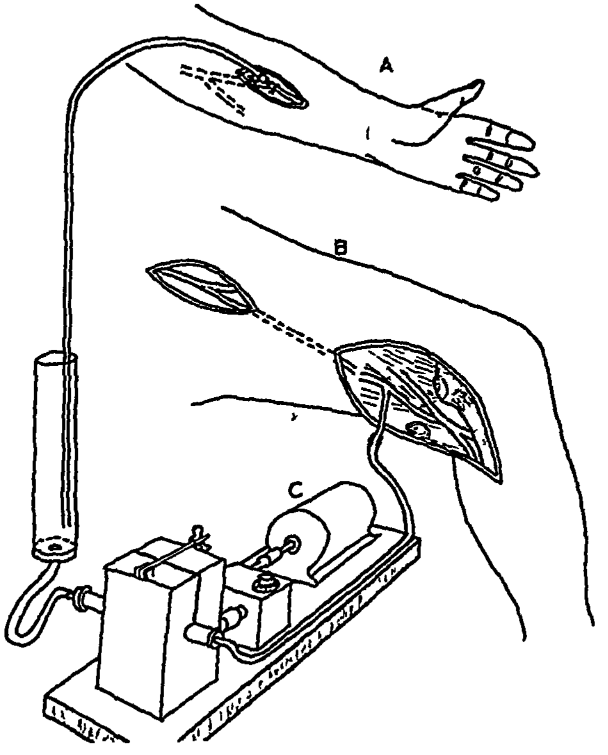

Fig 1—Cannulations made and apparatus

A shows a vein in the antecubital fossa cannulated centripetally Blood is drained into the cylindrical reservoir

B shows the vessels exposed in leg, with the upper graft anastomosed to the common femoral artery (in the upper incision) The interrupted double line represents the graft lying beneath the fascia in the thigh The lower graft has been anastomosed to the popliteal artery (lower incision), and the side branch has been cannulated to receive blood from the 'Sigma' pump (C) It only remains to anastomose the two free ends of the grafts

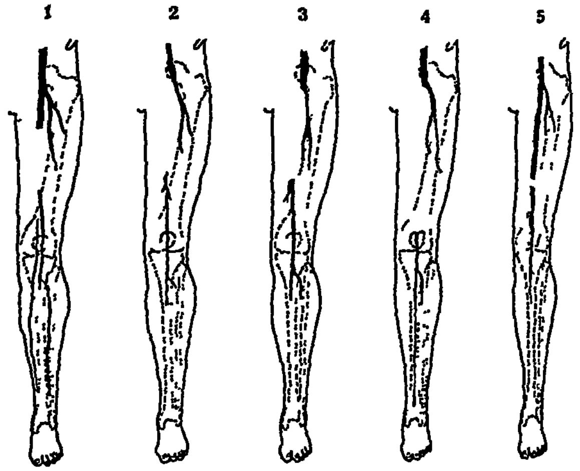

Fig 2—Result of arteriography and extent of disease in cases 1-5 whose legs were perfused

The disease in cases 1 and 5 was on the right side, but for the purpose of comparison it is shown as if it were in the left leg X-rays of the lower leg and ankle were not taken in cases 2 and 3 The distal vessels are most severely affected in case 5 See table II

Trial

It was thought that if the circulation through the smaller distal vessels of the limb could be maintained artificially while the main artery was occluded during the insertion of the graft, the chances of a successful outcome might be greater

With perfusion, restorative operations might be extended to cases shown on arteriography to have such severe peripheral disease, which otherwise would be classed as unsuitable

Methods

Principle

An intravenous dose of heparin is given to prevent clotting A vein in the antecubital fossa is cannulated, and from this venous blood is conducted into a reservoir (fig 1) Blood is pumped from here into the artery below the occlusion The venous blood used for perfusion is about 60% saturated with oxygen, but the saturation may be increased by heating the limb Copious bleeding is ensured by a sphygmomanometer cuff placed around the arm, inflated to 60 mm Hg Venous return from the perfused limb is via the natural channel—the leg veins

Apparatus

The venous cannula is flexible, consisting of a rigid nylon tube which is inserted into the vein, connected to a solid turned nylon adaptor by a flexible, clear polyvinyl-chloride (P V C) tube (Drew et al 1957) The diameter may be 4–6 mm The adaptor is inserted into a $^3/_4$ in (6 0 mm) internal-diameter P V C hose which leads to a reservoir The reservoir is a cylinder of rigid P V C and is of $1^1/_2$ in (37 0 mm) internal diameter

TABLE II—CLINICAL FEATURES, OPERATION DETAILS, AND RESULTS OF PERFUSION IN 6 CASES OF ARTERY-GRAFTING

Case no	Age (yr)	Extent of disease (arteriography, fig 2)	Pulses (preop)				Operation	Perfusion			Pulses (postop)				Remarks	Result
			F	Pop	P T	D.P		Duration (min)	Rate (ml. per min.)	Site	F	Pop	P T	D.P		
1	52	Rest pain Claudication at 100 yd. Femoral artery blocked Severe disease of anterior and posterior tibial vessels	±	—	—	—	Bypass graft, common femoral to popliteal, graft 38 cm. long	90	80–120	Lower graft	—	—	—	—	Breakdown of perfusion caused longer perfusion-time	Satisfactory
2	57	Intermittent claudication at 50 yd Occlusion of femoral artery	—	—	—	—	Bypass graft, common femoral to popliteal, graft 38 cm. long	? 100	90	Lower graft	+	—	—	—	Has graft functioning on other leg	”
3	51	Gangrene of great toe. Rest pain and claudication. Femoral artery occluded	—	—	—	—	Bypass graft, common femoral to popliteal, graft 44 cm. long	60	270	Lower graft	—	—	—	—	Previously unhealed great toe amputation healing	”
4	60	Wet gangrene of 4th and 5th toes Severe rest pain. Femoral and popliteal arteries blocked. Patent but severely diseased posterior tibial artery	—	—	—	—	Bypass graft, common femoral to popliteal, graft 40 cm. long	50	50	Lower graft	—	—	—	—	Amputation 4th and 5th toes	”
5	47	Anæsthesia of toes Severe rest pain. Block 1 cm. long of mid-femoral artery but severe disease of anterior and posterior tibial arteries	—	—	—	—	Bypass graft, common femoral to popliteal, graft 35 cm. long	40	150	Lower graft	—	—	—	—	—	”
6	69	Ruptured aneurysm common and external iliac arteries	—	—	—	+	Bypass graft, common iliac to external iliac, exclusion of aneurysm, graft 15 cm long	60	60	Inf epigastric artery	+	+	—	—	—	”

F = femoral Pop = popliteal P T = posterior tibial D P = dorsalis pedis
The return of pulses after operation is sometimes delayed for several days Absent distal pulses are quite compatible with relief of symptoms (case 5)

From the bottom of the reservoir a $^1/_4$ in (6 0 mm) P V C. hose leads to a Sigma or deBakey type pump, and a similar hose connects the pump to the arterial cannula which, like the venous one, is flexible

Technique of Bypass Grafting from Common Femoral to Popliteal Artery

The clotting-time of the blood is estimated by the method of Dale and Laidlaw (1911) The anæsthetised patient lies supine on the operating-table with diseased leg abducted and externally rotated at the hip and flexed at the knee The popliteal artery is approached through an incision on the medial aspect of the leg The insertion of gracilis, sartorius, and semitendinosus is divided The medial head of the gastrocnemius, and if necessary that part of the soleus origin which is attached to the soleal line on the tibia, are divided and displaced backwards

The patent vessel below the block is incised, and any atheromatous deposits are removed until a free " bleed-back " from the distal end of the artery is observed.

The assistant meanwhile reconstitutes two freeze-dried homografts of such combined length as to span the distance from the common femoral to the popliteal artery Each consists of the common, external iliac, and upper femoral arteries All the side branches are tied off or sutured except the internal iliac branch, which is left about 1 in (2 5 cm.) long The surgeon then anastomoses the end of one of the grafts to the opening in the popliteal artery While this anastomosis is being made, the patient is heparinised with heparin 1 mg per kg body-weight. The assistant cannulates the basilic or median cubital vein centripetally The apparatus is charged with blood from the patient until the arterial cannula is filled, and the arterial cannula is inserted into the internal iliac branch of the graft and tied in The free end of the graft is temporarily closed by a bulldog clip and the perfusion started. The surgeon is now free to continue the operation secure in the knowledge that the patency of the lower graft, the leg vessels, and the anastomosis between them is assured by a stream of heparinised blood.

A separate vertical incision in the groin exposes the common femoral artery and its two terminal branches—the profunda and superficial femoral arteries If necessary, the external iliac artery can be exposed through an additional wound The common femoral artery is clamped, and the natural blood-supply to the limb is now cut off except for that entering it by the cruciate anastomosis via the buttock, and until the completion of the operation the nutrition of and the blood-flow in the limb depend almost entirely on perfused blood. This period may be as long as an hour according to circumstances Without perfusion the limb would be almost totally ischæmic, during this time.

An incision is made in the common femoral artery, and here again extensive atheromatous deposits may need to be removed. An end of the second graft is anastomosed to this incision, taking as much time as is necessary to ensure a perfect suture line The lower end of the upper graft is passed down the thigh under the fascia to emerge in the lower wound. Redundant graft is excised, and the two free ends of the grafts are joined (fig 1) The perfusion is stopped. The arterial cannula is removed from the side branch of the lower graft, which is temporarily clamped. The bulldog clip on the upper end of the lower graft is released and reapplied just below the side branch. The main vessel is momentarily released, and a jet of blood washes out any clot in the upper graft. The side branch is tied off and the bulldog clip removed. Finally the upper clamp is taken away, thus re-establishing the circulation. The wound is closed by replacing muscle origins and suturing the deep fascia with catgut No drains are used The clotting-time is measured and sufficient protamine sulphate given to restore it to normal

Results

The perfusion technique has been used on six patients The arteriograms of five of them (fig 2) show the extent of the disease. Case 6, with a dissecting aneurysm of the common iliac artery, did not undergo arteriography since clinical examination sufficed.

Table II expresses briefly the clinical condition of the patients before and after the operation and gives some of the operation and perfusion details There were no failures

Conclusion

While this study covers only a few cases, the results are encouraging The perfusion technique interferes in no way with the operation and does not seem to have any disadvantages The risk of hæmorrhage is not increased, no difficulty has been experienced in securing a sound anastomosis, and hæmorrhage from the wound during the operation has not been troublesome At the end of the operation the clotting-time is restored to normal with protamine, no further anticoagulants are used, and in no case has postoperative hæmorrhage occurred

In table I one other patient is shown to have had a graft inserted He had a duodenal ulcer and was not perfused because of the supposed risk of hæmorrhage from his ulcer under the influence of heparin (Rains et al 1957) His graft thrombosed and ultimately he lost his limb

In the future a similar perfusion method can be adapted to maintain the vitality of both limbs in cases of aortic aneurysm Further, this method has an application in the treatment of the acutely ischæmic limb before restoring the circulation by washing out the products of tissue ischæmia Thompson and Campbell (1959) have shown experimentally how this may be possible The perfusate of dextran taken from the femoral vein is discarded and any tendency towards the "crush syndrome" (acute renal failure) averted (*Lancet* 1959)

It is also possible that an isolated neoplasm of a limb or organ could be effectively treated by perfusion of alkylating agents (Creech et al 1958)

We would like to thank the members of the heart-lung team—Prof A L d'Abreu, Mr L D Abrams, Mr J Fejfar, and Mr R Lightwood—for their help

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THYROID ACROPACHY

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THYROID acropachy is one of the more odd manifestations of endocrine disorder, and how or why it arises is not at all clear The changes consist in clubbing of the fingers and toes, periosteal new bone formation involving the phalanges and other distal long bones, and swelling of the soft tissues of the extremities, especially those overlying the affected bones (figs 1 and 2) These changes are nearly always associated with past or present hyperthyroidism, exophthalmos, and pretibial myxœdema The disorder seems to be rare, judging by the few reported cases, but this apparent evidence of rarity is probably misleading because the condition is often rather inconspicuous and usually causes no symptoms or disability

I describe here six cases and compare the findings with those in thirteen others previously reported (see table)

Case-reports

Case 1 —Man, aged 61 Hyperthyroidism with exophthalmos began in 1949, thyroidectomy was done the following year. He was well for a year, but in 1951 pretibial myxœdema began to develop, and this grew steadily worse as did his exophthalmos He also became hypothyroid and has required thyroid gr 2 daily since 1952 Various treatments were tried for the pretibial myxœdema without effect, this and the exophthalmos have not changed since 1952 Early in 1955 he noticed painless swelling in both hands, the swelling increased for a few months and has remained unchanged since

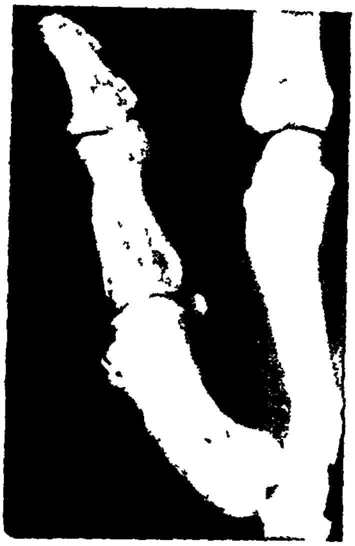

Fig 1—Case 1 X-ray showing characteristic new-bone formation in acropachy, most pronounced on extensor surface of first metacarpal

The changes of acropachy was more pronounced than in the other five cases The fingers and toes were clubbed Periosteal bone changes (fig 1) were present in the metacarpals, metatarsals, phalanges, and distal ends of the radius, ulna, tibia, and fibula There was considerable swelling of the soft tissues overlying the affected bones (fig 2) The joints were unaffected, and there was no muscular wasting, the affected parts were painless and not hot Apart from exophthalmos there was no change in the tissues of the face The serum calcium was 7 9 mg per 100 ml , phosphorus 5 0 mg per 100 ml , alkaline phosphatase 5 5 King-Armstrong (K.A.) units Erythrocyte-sedimentation rate (E S R.) 16 mm in the first hour (Westergren) Skull X-ray normal

Case 2 —Woman, aged 49 Hyperthyroidism and exophthalmos began in 1955 and thyroidectomy was done in April, 1956 Three months later hypothyroidism became evident and thyroid was started, gr 1 (later gr 3) daily, this has been continued up to the present time Pretibial myxœdema began to appear within a month of operation and steadily increased, exophthalmos also progressed In January, 1958, prednisone was given on account of increasing exophthalmos, this produced a temporary decrease in both exophthalmos and pretibial myxœdema, but after about three weeks, while high dosage was continued, both relapsed and became worse than ever Orbital decompressions were performed by Mr Harvey Jackson in March and April, 1958, with very good results Changes of thyroid acropachy were first noticed in June, 1958, and have become more pronounced since.

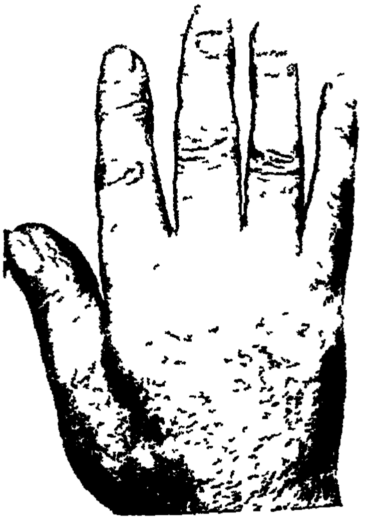

Fig 2—Case 1 clubbing and soft-tissue swelling, particularly over first two metacarpals

The fingers and toes were clubbed There was pronounced soft-tissue swelling of the hands, less localised to the parts overlying affected bones than in case 1 Periosteal new-bone formation was present in the metacarpals and phalanges, but the X-ray changes were slight compared with those in case 1

FINDINGS IN 19 CASES OF ACROPACHY

Case	Age (yr) at onset of acropachy	Sex	Pretibial myxœdema	Exophthalmos	Past or present hyperthyroidism	Thyroid state at onset of acropachy	Time from onset of hyperthyroidism to acropachy (yr)	Clubbing	Soft-tissue swelling	Radio-logical change
Present series										
Case 1	61	M	+	–	–	Hypo-	6	–	+	+
Case 2	47	F	+	–	+	Hypo-	3	+	–	–
Case 3	51	F	–	–	–	Eu-	12	–	–	–
Case 4	57	F	+	–	+	Eu-	8	–	+	–
Case 5	62	F	+	–	–	Hypo-	>13	–	+	–
Case 6	38	F	–	–	–	Hyper-	10	–	+	–
Reported cases										
Thomas (1933)	22	M	–	–	–	Hypo-	3	–	–	+
Cushing (1937)	37	M	–	–	+	Hypo-	8	–	+	+
Rynearson and Sarcasa (1941)	43	M	–	–	+	Hypo-	6 52	–	–	+
Greene (1951) 1	73	M	–	–	+	Eu-	10	–	–	–
” ” 2	?	M	–	+	–	Eu-	?	+	±	–
Levitt (1953)	?	M	–	–	–	?	?	–	–	+
Engel (1953)	41	F	–	–	–	Hypo-	2	–	–	–
Inch and Rolland (1953) 1	38	F	–	+	–	Hypo-	“ soon ”	+	–	–
” ” ” ” 2	36	M	+	–	+	Eu-	16	–	±	–
McGill (1957)	51	M	–	–	–	Eu-	3	–	±	–
Freeman (1958) 1	56	M	–	+	–	Hypo-	28	–	–	–
” ” 2	54	M	–	+	–	Hyper-	3 12	–	–	–
Diamond (1959)	24	M	+	–	–	Eu-	4	–	+	+

Some stiffness and discomfort in the hands developed after the acropachy appeared, there was no evidence of arthritis or muscular wasting, but there was some loss of power in grip In the face there was no change other than residual effects of “ mooning ” from prednisone The serum calcium was 10 6 mg per 100 ml., phosphorus 3 6 mg per 100 ml , alkaline-phosphatase 9 K.A. units E.S.R. 10 mm in the first hour ^{131}I uptake by the thyroid was very low and was unaffected by thyroid-stimulating hormone given in two doses each of 10 units after three weeks without thyroid treatment Forearm blood-flow estimated by venous occlusion plethysmography was found to be normal The urinary œstrogen excretion was within normal limits Skull X-ray was normal Precipitin and agglutination tests on the patient's serum with thyroid antigen were negative

Case 3 —Woman, aged 51 Thyroidectomy was done in 1946 on account of hyperthyroidism with exophthalmos Soon after operation pretibial myxœdema began to appear and increased steadily despite many attempts at treatment, finally it became very severe and extensive Since 1954 it has changed little. Exophthalmos also increased for several years after thyroidectomy and some ophthalmoplegia developed, later both regressed a little The patient has been euthyroid since thyroidectomy

The hands were inspected from time to time for changes of acropachy There was nothing abnormal until July, 1958, when clubbing of the fingers was noted There was also some soft-tissue swelling of the hands, but no periosteal new-bone formation was detected in X-rays of the hands The serum calcium was 9 1 mg per 100 ml., phosphorus 4 9 mg per 100 ml , E.S.R. 20 mm. in the first hour

Case 4 —Woman, aged 58 Thyrotoxicosis without eye signs developed in 1950 Thyroidectomy was done in 1951, and soon afterwards exophthalmos and pretibial myxœdema developed The exophthalmos never became severe, the pretibial myxœdema advanced slowly with fluctuations but has never become extensive In 1957 thyrotoxicosis recurred and was treated with radio-iodine, there was no change in exophthalmos and slight increase in pretibial myxœdema Changes of thyroid acropachy were first noticed in 1958

There was no clubbing of the fingers, but there was periosteal new-bone formation and overlying soft-tissue swelling which involved the first metacarpal obviously and was possibly present elsewhere in the hands The condition was symptomless The localisation of the changes of acropachy in this patient are notable, the absence of clubbing is unusual but has been described before (Diamond 1959) Otherwise the changes were quite typical Serum calcium 10 4 mg per 100 ml , phosphorus 3 0 mg per 100 ml , alkaline-phosphatase 6 K.A. units, E.S.R. 7 mm. in the first hour

Case 5 —Woman, aged 62 Hyperthyroidism developed 1944 and was treated by thyroidectomy, subsequently t patient became hypothyroid and has taken gr 2 of thyro daily since. Moderate exophthalmos developed soon aft operation and has been unchanged since Pretibial myxœder began to appear on the left leg eight months after operatio became bilateral, and has gradually progressed and becor severe The patient noticed swelling over the second le metacarpal after minor trauma in 1957 When acropachy w first present is uncertain, it causes no symptoms The finge are clubbed, and periosteal new-bone formation and soft-tiss swelling, notably patchy in distribution, involve the met carpals and phalanges Precipitin and agglutination tests o the patient's serum with thyroid antigen were negative

Case 6 —Woman, aged 36 Hyperthyroidism develope in 1955 and was treated by thyroidectomy Moderate exop thalmos was present before thyroidectomy and has not great changed since. Pretibial myxœdema appeared a few mont after thyroidectomy and became moderately severe Hype thyroidism recurred in 1959 and was treated with radioacti iodine. It was noted then that the fingers were clubbed ar the soft tissues of the hands thickened. There was very slig periosteal new-bone formation.

Discussion

Acropachy is the last and rarest part of a syndrom *the other parts being hyperthyroidism, exophthalmo* and pretibial myxœdema, usually arising in that orde The changes have been thought to be due to a disord of hormone secretion by the anterior pituitary, and in tw patients with acropachy eosinophil hyperplasia or adenom has been described (Freeman 1958) In the present seri skull X-rays showed normal pituitary fossæ Possibl autoimmunisation plays a part, but so far there has bee no positive evidence. The great majority of describe cases of acropachy have been in males

Why the syndrome of Graves' disease with pretibi myxœdema and acropachy should develop piecemeal ove a variable and often long period is obscure In the case described here and in other reports, the changes o acropachy have invariably been found in association wit other features of the syndrome, usually all of them, an acropachy has not been described as occurring alone o in any other condition Acropachy usually appears som time after the other components of the syndrome whe hyperthyroidism has been treated, and it is therefor rarely present with active hyperthyroidism as in case and in a case reported by Freeman (1958) The interva between the onset of hyperthyroidism and the recognition of acropachy varied from a few weeks to twenty-eight years (see table) Hyperthyroidism has been recognised at some stage in all patients with acropachy except one (Greene 1951), exophthalmos has been present in all, and pretibial myxœdema in the majority

The changes in thyroid acropachy seem to be unique, and the question of differential diagnosis hardly arises In some of the earlier described cases there was confusion with hypertrophic pulmonary osteoarthropathy In acropachy the periosteal bone changes are quite different in appearance they simulate bubbles on the bone surface, and they are differently situated, being on more peripheral parts of the skeleton Also the characteristic heat, pain, and evidence of increased bone blood-flow (Ginsberg 1958) in pulmonary osteoarthropathy is absent in acropachy The soft-tissue thickening of acropachy is an important diagnostic feature, particularly when localised over the affected bones In acromegaly, occasionally associated with hyperthyroidism, the changes in the hands and elsewhere should not be confused with those of acropachy, although some new bone formation occurs There is a rare familial condition—idiopathic osteodystrophy or pachydermoperiostosis (Angel 1957) in which clubbing and thickening of the tissues of the hands, feet, and face develop early in adult life This condition has some resemblance to acropachy, but it is not associated with other features of the acropachy syndrome

Symptoms from thyroid acropachy are unusual, and treatment is therefore not an important problem There may be complaint of stiffness due to generalised soft-tissue swelling of the hands, but the joints do not seem to be involved, and there is no evidence of muscular weakness or wasting The natural course of thyroid acropachy is uncertain, in some patients there has been no change for several years, possibly, as with other features of Graves' disease, partial or complete remission may occur naturally after a time

The frequency of thyroid acropachy is very difficult to determine since it may appear so many years after the onset of thyrotoxicosis that an ordinary follow-up would be inadequate The present series of six cases were met with over a period of four years during which there were about five hundred new cases of hyperthyroidism Possibly acropachy eventually develops in about 1% of patients with hyperthyroidism

Thyroid acropachy must be added to the long list of miscellaneous conditions associated with clubbing, and the changes in acropachy are not readily explained by any of the mechanisms or causes of clubbing which have been suggested in certain other disorders

Summary

Six cases of thyroid acropachy are described Acropachy consists of clubbing of fingers and toes, distal periosteal bone change, and swelling of the overlying soft tissues

The condition arises occasionally as a final phase of development of the acropachy syndrome of hyperthyroidism, exophthalmos, and pretibial myxœdema

The cause of acropachy is obscure, but apparently in some circumstances certain of the peripheral tissues undergo peculiar changes, possibly under the influence of a pituitary hormone

I am grateful to Dr H K Goadby, Prof E P Sharpey-Schafer, Dr J S Richardson, Dr H J Anderson, and Dr H J Wallace for permission to describe cases under their care

References at foot of next column

PREGNANCY AFTER TUBERCULOSIS OF THE FALLOPIAN TUBES

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Rabau first reported a pregnancy after the successful treatment of proved endometrial tuberculosis in 1952, and several other cases have been described since We have been unable to find any reference to proved tubal tuberculosis followed by pregnancy, although in one of Earn's (1958) cases of endometrial tuberculosis the left fallopian tube was palpable at the first examination We therefore present the following case-report, which shows that pregnancy is possible after tuberculosis of the fallopian tubes has been treated medically

Case-report

The patient, aged 25, who had been married 9 months, was referred, on June 29, 1955, to S W L with suspected extra-uterine pregnancy Her last normal menstrual period was at the end of April—i e, 8–9 weeks previously From the last week in May until the time of examination she had had irregular vaginal bleeding, and had passed occasional small clots She also had cramp-like lower abdominal pain She denied any previous serious illness or familial tuberculosis, although 2 weeks later her mother underwent nephrectomy for renal tuberculosis

Examination

She seemed to be healthy and was of medium build Her heart and lungs were normal, and the temperature and pulse-rate were not increased The abdomen moved easily on respiration, no tumour was felt but there was slight tenderness on both sides of the lower abdomen Bimanual examination revealed a slightly enlarged uterus and an irregular, slightly tender mass, which appeared to be fixed to the uterus, in the pouch of Douglas

The patient was admitted to a nursing home for observation because the diagnosis was in doubt On June 30 her condition was unchanged, but next evening she had fairly severe abdominal pain She was not in a state of shock and she had no signs of intra-abdominal bleeding Because the mass in the pouch of Douglas was more tender, an examination under anæsthesia and possibly laparotomy was planned for next morning

Operation and Course

Under general anæsthesia (July 2) the previous findings in the pelvis were confirmed As an ectopic pregnancy could not be excluded, laparotomy was performed through a midline sub-umbilical incision The omentum was adhering to the uterine fundus and covering the pelvis When this was freed the uterus was found to be enlarged to the size of a *6–8 weeks* pregnancy by multiple small fibroids The mass in the pouch of Douglas comprised the swollen and inflamed fallopian tubes The left tube was distended to at least 1 in diameter, and the right to about ¹/₂ in, thin yellow pus was escaping from their fimbrial

DR GIMLETTE REFERENCES

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ends, from which a swab was taken for examination. The abdomen was closed without drainage, and the patient returned to the ward in good condition.

Direct microscopical examination (J. A. L. J.) showed pus-cell debris and necrotic material with some intact leucocytes and lymphocytes, and a few giant cells. No gram-positive organisms or acid-fast bacilli were seen, but a tuberculous infection was suspected. Culture of the pus for these organisms was arranged.

By the 3rd postoperative day the patient had a temperature of 102°F, with a corresponding tachycardia. That evening she had a hæmoptysis, and was examined by J. A. L. J. The heart sounds and rhythm were normal, and the blood-pressure was 120/80 mm. Hg. The patient said she had had a pain in the left axilla at the level of the 6th or 7th rib, some 36–48 hours before the hæmoptysis. A slight friction rub and a few crepitations were heard in the left submammary area. The respiratory rate was increased, but deep breathing did not cause pain. Sputum (3 specimens) was negative for tubercule bacilli.

A small pulmonary embolus was diagnosed provisionally, but in view of the abdominal findings the possibility of pulmonary tuberculosis was considered, and treatment with streptomycin and isoniazid was instituted. The pyrexia and tachycardia disappeared in 3 weeks, and chest radiographs on July 18 showed a very small effusion within the left pleural cavity, but the rest of the lung fields were clear. A further radiograph on Aug. 3 showed that the left costophrenic sinus was clear, although increased density in this area persisted. Convalescence was uneventful, and the patient was allowed home in mid-August, her medical treatment being continued.

When reviewed on Sept. 10, the patient's general condition had improved, although pyrexia (99·6–100·4°F) had returned, with some sweating. Her weight had increased by $4^1/_2$ lb. Radiographs showed no active lesion in the lungs, but a large calcified abdominal gland was noticed. The hypogastrium was tender.

The results of the bacterial cultures became available. Blood-agar plates were sterile after 4 days' incubation, but after 7 weeks on Lowenstein and Jensen medium typical colonies of tubercle bacilli were present. Acid-fast and alcohol-fast tubercle bacilli were seen microscopically. Examination of the blood showed hæmoglobin (Hb) 90%, red blood-cells 4,000,000 per c.mm., white blood-cells 11,000 per c.mm., hæmatocrit 35%, erythrocyte-sedimentation rate (E.S.R.) 10 mm. in the 1st hour (Westergren). Streptomycin therapy was replaced by *p*-aminosalicylic acid, and isoniazid was continued.

On Oct. 12 the patient's temperature was lower and her weight had increased. By Nov. 1 her temperature was normal apart from an occasional spike, and the E.S.R. had fallen to 7 mm. in the 1st hour. Her condition remained unchanged for several weeks, but by Dec. 28 a definite pattern of pyrexia was apparent during the progestational phase of the menstrual cycle. Her weight had increased further but the E.S.R. had risen slightly to 11 mm. in the 1st hour, and the hæmatocrit had fallen to 36%.

Menstruation had returned in September, without pain or intermenstrual bleeding. On Jan. 30, 1956, no abnormality was detected in the abdomen, and on vaginal examination the uterus seemed normal. The right fallopian tube could not be felt, but the left was still much enlarged and thickened.

On Feb. 3 the E.S.R. was 18 mm. in the 1st hour, Hb 84%, and hæmatocrit 36%. No lung lesion was found clinically or radiographically. The patient was readmitted to the nursing home for complete rest, and further streptomycin was given. By March 9 her condition had improved considerably, and she was allowed to go home. She still had pyrexia in the progestational phase of the menstrual cycle, but it now never rose above 99°F. The E.S.R. was 11 mm. in the 1st hour, Hb 88%, and hæmatocrit 36%, her weight had increased to 11 st. 10 lb.

First Pregnancy

The improvement continued, but on May 23 she complained of some dizziness, and although no 8th nerve lesion was detected streptomycin was discontinued as a precautionary measure. On June 6 menstruation was 14 days overdue, and pregnancy was confirmed by a positive Hogben test in mid-July. By the end of July, because she was much troubled by vomiting, the *p*-aminosalicylic acid was replaced by streptomycin. On Aug. 3 she aborted incompletely a ten-week fœtus. Next day, at curettage under general anæsthesia, several fibroids were palpated. Convalescence was complicated by a thrombophlebitis of the right internal saphenous vein. Menstruation returned on Sept. 9. On Sept. 29 the E.S.R. was 10 mm. in the 1st hour.

At postoperative review on Oct. 4 the right leg showed no sign of the previous thrombosis. The cervix was healthy, and the uterus and fibroids were well involuted. She had slight dysuria, but no cause was found.

At the end of October dizziness and tinnitus had returned, but the E.S.R. was 8 mm. in the 1st hour, and her general condition was good. Streptomycin was stopped, and all other treatment was scaled down. She was not seen again until March 8, 1957, when she had had no treatment for about 2 months. She was well, her weight had increased, and the E.S.R. was 3 mm. in the 1st hour.

Second Pregnancy

At the end of May she again reported that menstruation was overdue (last menstrual period April 16) and a Hogben test confirmed pregnancy. In view of the previous miscarriage 6 (25 mg.) pellets of progesterone were implanted deep to the fascia lata. She was again given *p*-aminosalicylic acid.

Pregnancy proceeded normally (blood-pressure 120/80 mm. Hg, no albuminuria) until Sept. 9, when decalcification of her teeth was noted. She was given calcium and vitamin D, and for the next 2 months she seemed to be normal.

Just before Christmas her right leg had been swollen for 5 days but had improved since. On Jan. 3, 1958, slight œdema was found, but no evidence of any clot formation. The blood-pressure was 130/80, a trace of albuminuria was found, and the fœtal heart was heard. The fœtal head had not engaged in the pelvic brim. The patient was advised to rest.

On Jan. 10 the blood-pressure had risen to 150/90 and the urine still contained a slight trace of albumin. The fœtus was presenting by the vertex, and the fœtal heart was heard. The patient was advised to continue resting at home. She was admitted to the nursing home on Jan. 17 as she feared she might be isolated at her home in the country by a snow storm. With complete rest in bed the blood-pressure fell to 140/90 and the urine became albumin-free.

Labour started spontaneously on Jan. 28—i.e., 285 days after the first day of her last menstrual period. Progress was very slow, with weak irregular pains, after 36 hours the cervix was only three-fingers dilated, and the head was still free. In view of the length of labour, the uterine inertia, and the non-engagement of the head, a lower-uterine-segment cæsarean section was performed on Jan. 29, and a live female infant weighing 10 lb. was delivered. At operation cephalopelvic disproportion was noted, and the fibroids were still present, but both fallopian tubes looked normal, without evidence of previous disease. There was a large placental infarct, and the liquor was heavily stained with meconium.

Convalescence was uneventful at first. Careful and regular examinations showed no evidence of venous thrombosis. The patient got up daily from the 3rd day, and moved about her room. On the 10th postoperative day, while she was cleaning her teeth in the bathroom, she collapsed from a pulmonary embolus, and despite morphine and intravenous heparin she died 20 minutes later. The infant has progressed satisfactorily.

Discussion

Despite this patient's unfortunate death her history shows that in cases of tuberculous salpingitis the radical and surgical treatment previously practised by Stallworthy (1952) and others may no longer always be necessary, and that with present-day medical treatment even considerable damage to the fallopian tubes by tuberculous disease does not always mean sterility.

This case was treated along the lines recommended by Hallum and Thomas (1955) and Norburn and Walker (1956) with the addition of isoniazid 100–150 mg daily As in Rabau's case, the first pregnancy after treatment ended in early abortion We do not think the post-operative thrombophlebitis was necessarily associated with the tuberculous infection

Summary

A patient with tuberculosis of the fallopian tubes, treated medically, had afterwards two pregnancies which resulted in an abortion and a healthy infant

At the time of the cæsarean section both fallopian tubes were free from macroscopic signs of inflammation

Three consecutive operations were followed by venous thrombophlebitis The third proved fatal because of pulmonary embolism

We wish to thank Dr D S Wilson and Lieut -Colonel D G C Whyte, D S O , for their assistance with the anæsthesia and radiology, and Miss E Scott, S R N , S C M , and her staff for nursing the patient

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STERNAL TRACTION FOR THE FLAIL CHEST

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Since Jones and Richardson (1926) first described a method of controlling paradoxical respiration after chest trauma by skeletal traction on the sternum, using a gynæcological " bullet forceps ", several reports have suggested other methods and instruments found valuable

Butler (1938) and Williams (1948) advocated the use of towel-clips to grasp the ribs, Jaslow (1946) used coat-hanger hooks screwed into the sternum. All three workers employed weight traction

Proctor and London (1955) used " cup hooks " in the sternum fixed to a special bed frame, while Heroy and Egglestone (1951) made drill holes in the sternum and applied a clamp and 10 lb traction Ritter and Kaye (1944) used perichondral wires with weight traction. Other workers have advocated open reduction of sternal fractures and fixation with plates (Hendry 1957) or crossed Kirschner wires (McKim 1943), and finally Coleman and Coleman (1950) suggested open reduction of the multiple rib fractures and fixation with wire sutures Birchfield and Grant (1956) also recommended this method of managing the " stove-in " chest

Recently for sternal fixation in a patient with multiple injuries I used an instrument available in most traumatic centres—i e , a skull calliper—and found it to be both easy to apply and effective

Case-report

A man, aged 27, was involved in an accident at work in a textile factory on Jan. 6, 1959, when his right hand was trapped in a machine His arms, head, and trunk were drawn between the rollers, crushing him and at the same time enveloping him in several layers of fabric The machine had to be reversed to roll him out and he was removed from the wrappings unconscious, deeply cyanosed, and not breathing After artificial respiration by a workmate he regained consciousness On arrival in hospital, about half an hour after the accident, he was conscious but grossly shocked His pulse and blood-pressure were unrecordable, and although there was no cyanosis there was severe respiratory distress His injuries included compound fractures of the left humerus and left radius and ulna, a fracture of the ascending ramus of the mandible on the right, a fracture of the neck of the right scapula, fractures of the right radius and ulna, a subtrochanteric fracture of the right femur, and finally bilateral fractures of the second to ninth ribs inclusive in the anterior axillary lines (fig 1) The entire anterior chest wall, an area measuring about 135 sq in , was involved in paradoxical movement, and he showed the orbital hæmorrhages of traumatic asphyxia.

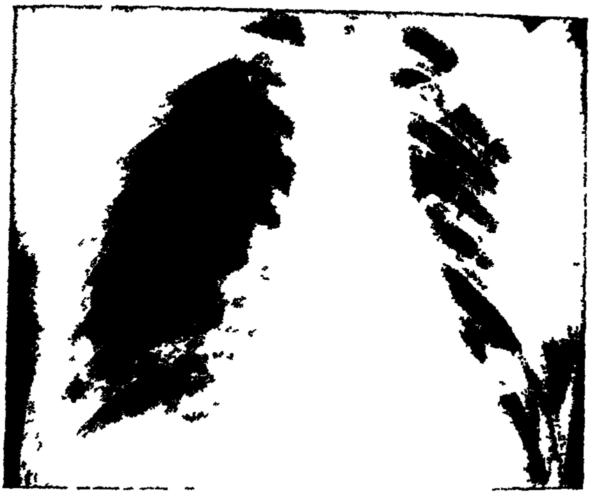

Fig 1—Chest radiograph on the day after injury, showing multiple bilateral rib fractures

After immediate splinting of the limb fractures, strapping the chest, and rapid infusion first of dextran and then of blood, his condition improved enough to allow operation, which was performed under general anæsthesia First the chest wall was

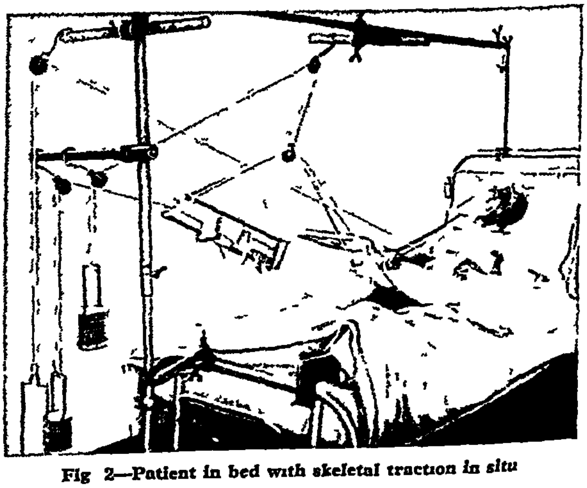

Fig 2—Patient in bed with skeletal traction in situ

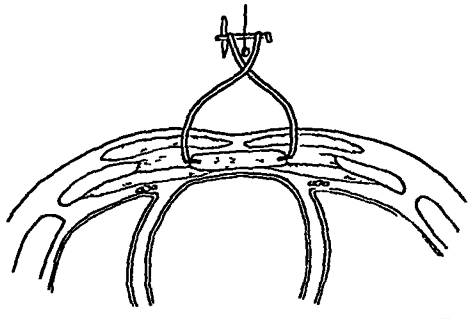

Fig 3—Diagrammatic cross-section of anterior chest wall at the level of the 5th intercostal space

enclosed in circumferential strapping, and then routine toilet and manipulation of the fractures was performed The limb fractures were immobilised in plaster After a total transfusion of 9 pints of blood his general condition was good, although, despite the strapping, there was still considerable paradoxical movement of the anterior chest wall

For three days the improvement was maintained, and then a " wet-lung syndrome " supervened and the patient rapidly deteriorated The respiratory rate rose to 60 per min and the pulse-rate to 160 per min. The hæmoglobin fell from 92% on the morning after injury to 80%, and the white-blood-cell count rose to 25,600 per c.mm. Fixation of the flail chest segment was regarded as essential, and this was carried out as follows

Under local anæsthesia, a transverse incision about 5 in long was made across the sternum at the level of the sixth costal cartilage The upper part of the rectus abdominis was divided, and the fifth intercostal space on each side was exposed by incising the anterior intercostal membrane A Crutchfield skull calliper was used to grasp the sternum, the prongs biting into the lateral edges of the bone between the fifth and sixth cartilages on each side The calliper was then tightened to gain a firm hold and traction of 14 lb was applied over pulleys (figs 2 and 3)

The patient's condition improved immediately and dramatically The respiratory rate fell to 30 per min. and the pulse-rate to 110 The cyanosis cleared, the pain in the chest was relieved, and the patient was able to cough But the paradoxical movement, though much reduced, was still present, and in fact could not be completely overcome even by pulling manually on the calliper with a much greater force With this increased pull there was some discomfort from the calliper, but with 14 lb there were no adverse symptoms The wound was finally closed round the calliper

Within twenty-four hours, the chest was clinically and radiographically dry, and thereafter the improvement was maintained On Jan. 17, again under general anæsthesia, with the traction still in place, open reduction of the two forearm fractures was performed. Even at this time temporary removal of the traction was followed by rapid return of respiratory distress, but by mid-February there was radiographic early union of the rib fractures, and the traction was discontinued without return of paradoxical respiration. Since then progress has been uneventful Apart from slight delay in the left forearm, the limb fractures have united satisfactorily, the patient's general condition is excellent, and there is no significant deformity of the chest wall

Discussion

With the increasing number of road accidents, " stove-in " chests are being seen more commonly, and are usually the result of crushing by the steering-wheel during collision The injury is frequently anterior and often involves the sternum as well as the ribs Furthermore, frequently there are other injuries, sometimes very severe

Although Hulman (1957) suggests that, in the management of such injuries, tracheotomy and bronchial aspiration are all that is required and gives physiological reasons for this, and Shefts (1956) states that " tracheotomy is almost mandatory ", there are disadvantages in this method—particularly the loss of the protective function of the upper air passages against infection Many surgeons, therefore, prefer to avoid tracheotomy if possible Open reduction of rib fractures, recommended in many centres, has the great disadvantage of converting a closed chest injury into an open one Coleman and Coleman (1950) and Birchfield and Grant (1956) both confirm that the parietal pleura is always torn below the rib fractures, and recommend routine intercostal drainage after operation Nevertheless the operation is a major one in a patient who may be in a grave state, as much from other injuries as from the thoracic lesion Furthermore the operation requires expert thoracic surgical skill and nursing, neither of which may be available in the traumatic centre to which the patient is first admitted

Other methods of skeletal traction have disadvantages Towel clips placed round ribs or pericostal or perichondral wires may, as Shefts (1956) says, injure the internal mammary artery in their application, and " not infrequently the pleura or the lung may be involved " Even if available, single screws in the sternum, cup hooks, and coat-hanger hooks are not mechanically sound Clamps fixed to the sternum through drill holes involve the risk of the drill perforating the posterior sternal plate and injuring the mediastinum

Moreover, with involvement of a large area of chest wall in the paradoxical movement, the forces required to stabilise the flail segment are relatively great Although Cooper (1957) found $2^1/_2$ lb traction effective, in this case not even 14 lb was enough to control the flail segment completely In normal quiet respiration the difference in negative pressure in the pleural cavity between inspiration and expiration is said to be 5 mm Hg, or about $^1/_{10}$ lb per sq in (Wright 1952) In flail chests, it is probably this decreasing negative pressure that causes the indrawing of the unstabilised segment of the thoracic cage on inspiration In this patient, therefore, a theoretical traction force of $13^1/_2$ lb should have controlled the anterior chest wall Nevertheless even a much greater force did not completely prevent some indrawing Presumably, therefore, the gross respiratory distress of a patient with a " stove-in " chest must result in an intrapleural pressure swing of much more than 5 mm Hg, and thus the traction force required is consequently increased

Thus very firm skeletal traction is required for adequate management of these cases The skull calliper allows such firm traction to be applied, and furthermore is simple to apply, with little risk The dissection required is not deep enough to involve the left pleural reflection, and the application of the clamp directly to the lateral edge of the sternum avoids the internal mammary artery which runs usually half an inch laterally Its use is therefore advocated in the management of flail chests when the sternal segment of the chest wall is part of the unstable section

Summary

In a man with severe multiple injuries a skull calliper was applied successfully to control paradoxical respiration in the flail chest These allowed firm traction to be applied, and, although indrawing of the affected segment was not entirely prevented, the improvement in the patient's condition was dramatic and immediate

I thank Dr J H Dixon, but for whose skilful anæsthetics this treatment could not have been carried out, Mr D M Dunn, who allowed me to treat this case in the early stages, for his help and encouragement in preparation of this paper, and Miss M Fishwick for fig 3, and the photographic department of the Royal National Orthopædic Hospital for fig 1

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THROMBOTIC THROMBOCYTOPENIC PURPURA

REMISSION ON TREATMENT WITH HEPARIN

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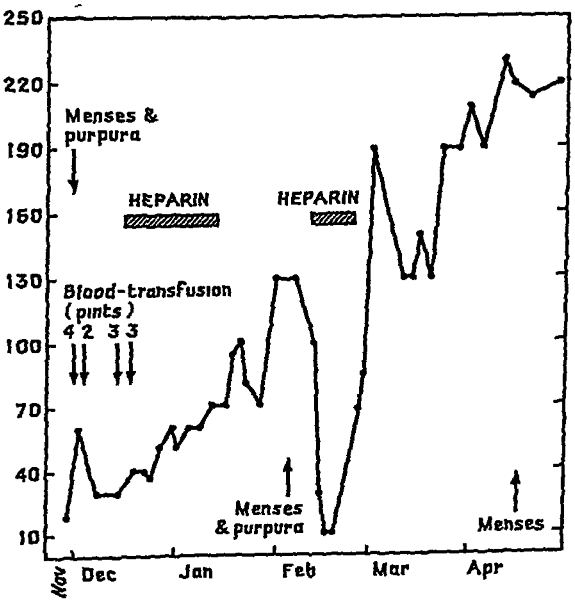
Since the original description of thrombotic thrombocytopenic purpura by Moschowitz (1924, 1925), about a hundred cases have been reported Although in the clinical presentation considerable variation has been noted, there is a diagnostic syndrome of acute febrile hæmolytic anæmia, thrombocytopenia, and transient neurological signs present at some stage of the disease The course is generally relentless and fatal We report here a case in which heparin apparently induced two remissions

Case-report

Mrs A , aged 27, was admitted on Nov 28, 1958, for an acute hæmorrhagic illness, with fever, severe anæmia, slight icterus and sore throat, and a raised erythrocyte-sedimentation rate 9 days previously she had had an acute upper respiratory infection, followed 2 days later by a sore throat, generalised purpura of skin and mucous membranes, and vaginal bleeding Sulphonamide and penicillin therapy had been given by her family doctor 5 weeks before this a urinary-tract infection had been treated with sulphonamides

Flexion in one knee was limited probably because of rheumatoid arthritis 4 years previously (This had been associated with hyperglobulinæmia [total protein 8 g per 100 ml globulin 4 g] and had been treated successfully with corticotrophin) The liver, spleen, and superficial lymph-nodes were not palpable, the retinæ, nervous system, and mental state were normal, and there was no abnormality of the cardiorespiratory systems Blood examination showed a hæmolytic anæmia with thrombocytopenia

Hæmoglobin 37% (5 4 g per 100 ml) Packed-cell volume 17% Mean corpuscular hæmoglobin concentration 32% Anisocytosis and poikilocytosis, many spherocytes and fragmented red cells Normoblasts 21 per 100 white cells, reticulocytes 21%, platelets 60,000 per c mm , white cells 16,900 per c mm (polymorphonuclears 69%, eosinophils 2%, lymphocytes 25%, metamyelocytes 4%) Many of the lymphocytes were early forms Coombs' antiglobulin and platelet antibody tests negative. Several preparations for L.E (lupus erythematosus) cells were negative and the serum proteins were normal (Total protein 7 g per 100 ml , albumin 4 5 g per 100 ml , globulin 2 5 g per 100 ml)



Marrow from the iliac crest showed hyperplasia of the normoblast series and no abnormality of the white-cell series Megakaryocytes were present in normal numbers but showed none of the cytoplasmic granularity usually associated with platelet production Wassermann reaction was negative A diagnosis of acquired hæmolytic anæmia with thrombocytopenia was made

Progress

On the 2nd day in hospital the patient developed paræsthesiæ and weakness of the right arm and face with slurred speech, and the diagnosis was altered to thrombotic thrombocytopenic purpura The hæmoglobin was now 22% (3 3 g per 100 ml.) and the platelets 30,000 per c mm Prednisone, 40 mg daily, was given for 2 days, and then increased to 60 mg with the addition of 40 units of corticotrophin daily 12 pints of blood, partly fresh, taken and administered through siliconed apparatus, was given to raise the low hæmoglobin and platelet levels The hæmoglobin level repeatedly reached 60% but always fell to pretransfusion figures in about 2 days

The general condition remained grave Purpura and vaginal bleeding continued, and once or more daily there were neurological episodes, lasting 2-12 hours, with stupor, paresis, and behaviour and mental changes

A feature of the blood-film at this stage was the daily variation in the number of spherocytes and fragmented red cells and the big variation in the number of primitive white cells

On the 20th day heparin therapy was started, with a small dose of 1000 units intramuscularly every 4 hours This did not increase coagulation-time, which was 7 minutes (Lee and White) After a day's heparin treatment there were no more neurological episodes, and by the 2nd day there was no fresh hæmorrhage, therefore the same dosage was continued. The hæmoglobin level and platelet-count rose steadily (see fig) without further blood-transfusions The white-cell count returned to normal levels although some primitive cells persisted, the reticulocytes fell and abnormal red cells disappeared

Corticoid therapy was slowly discontinued and heparin therapy was stopped after 4 weeks The patient was discharged ambulant and symptom-free with hæmoglobin 75% (10 9 g per 100 ml), and white cells 6200 per c mm (polymorph neutrophils 70%, eosinophils 4%, lymphocytes 25%, monocytes 1%) No abnormal red cells Platelets 105,000 per c mm Reticulocytes 4%

Second Episode

For 4 weeks she remained well In the 5th week her usual menstrual loss started, but it was heavier than usual and accompanied by a sore throat and purpura of skin and mucous membranes The hæmoglobin was 66% (9 1 g per 100 ml)—a drop of 9% in 3 days—and the platelet-count 130,000 She was readmitted and heparin therapy, without corticoids or blood-transfusion, was begun in the same dosage as before Next day the platelets had fallen to 30,000, but there was neither new purpura nor excessive vaginal bleeding Menstruation ceased 2 days later Treatment was discontinued on the 12th day, and she was again discharged free of symptoms or signs Since then, menstruation and dental extractions have been unaccompanied by excess blood loss or hæmatological changes

Present Condition

The patient remains free from symptoms or abnormal signs The most recent blood-count, 40 weeks after the completion of the second course of treatment, is hæmoglobin 84% (12 1 g per 100 ml), white cells 6700 per c mm (differential count normal), platelets 160,000 per c mm

Discussion

In the first episode therapy was multiple but remission followed administration of heparin. In treating the relapse only heparin was used. The patient's recovery on this treatment is noteworthy because spontaneous remission in thrombotic thrombocytopenic purpura has not been reported, and death is usual within a month of the onset.

Delbeke and Coussement (1956) described the case of a child of 7 years who survived for 5 months. Thrombocytopenia but not anæmia remitted on steroid therapy. A relapse, uninfluenced by intensive therapy, followed 2 months after discontinuing treatment. The case of Engel et al. (1947) in which splenectomy was performed, remitted for 3 months but died in acute relapse.

We have found no examples of classical thrombotic thrombocytopenic purpura running a chronic course. Protracted cases appear to fall into three groups.

Rapid termination has been reported after long and varied illness which at first lacked the characteristics of the disease (Laszlo et al. 1947, Fitzgerald et al. 1947, Biegelman 1951, Comess and Oyamada 1952).

The cases described by Brown and Norman (1946), Gendel et al. (1952), Fisher and Creed (1955), and Baez-Villasenor and Ambrosius (1957) appear to have been unclassifiable hæmatological disorders terminating in thrombotic thrombocytopenic purpura.

Gardner et al. (1951) and Meacham et al. (1951) recorded cases of acquired hæmolytic anæmias, responding to splenectomy, which in terminal illness showed the features of the syndrome.

We have been able to trace five non-fatal cases. Shapiro et al. (1957) reported a 32-month survival after splenectomy and corticoid treatment; evidence of hæmolysis persisted. Siegel et al. (1954) reported a complete remission of similar duration, also following splenectomy and steroid therapy; L.E. cells were demonstrated 7 months after operation. Rodriguez et al. (1957) have reported complete remission for a year following splenectomy, and Burke and Hartmann (1959) complete remission in two cases following very large dosage of corticoids.

Treatment with blood-transfusion and corticoids is customary, and splenectomy has been performed on a number of occasions. Only in the cases cited above has therapy been of possible value.

In 1947, at a time when no case had been diagnosed during life, Singer et al. suggested the use of heparin. The suggestion was repeated, without clinical trial, by Singer et al. (1950) and Hauser et al. (1951). We have been able to find only two cases in which heparin was used. Adelson and Stefanini (1952) gave heparin sodium 75 mg. intravenously 4-hourly but abandoned the treatment after 2 days, and Adelson et al. (1954) apparently used the same dosage unsuccessfully for the same time in the terminal stage of a short illness. Hence the case we present is the first in which heparin seems to have induced a remission.

The mode of action of heparin, as an anticoagulant, is controversial. It prevents the agglutination and disintegration of platelets and may remove thrombin, thus interfering with the formation of fibrin. O'Brien (1958) suggested that it acts by combining with Christmas factor, thus lengthening the coagulation-time.

Despite the hazards inherent in giving heparin in the presence of hæmorrhage, its use in thrombotic thrombocytopenic purpura has a basis in the pathology of the condition.

Gore (1950) suggested that the primary defect is a subendothelial collection of hyaline material in the capillaries; this substance projects into the lumen and is covered by healthy endothelium. With excessive hyaline deposition, rupture takes place, platelets are withdrawn from the circulation by deposition on the roughened surface, and clotting follows. Using fluorescein-conjugated antibody, Craig and Gitlin (1957) identified the hyaline thrombi as a derivative of fibrinogen or fibrin. The view that the condition is primarily associated with damage to capillaries and arterioles is stressed by Meacham et al. (1951), Orbison (1952), and March (1954).

Further evidence of the secondary nature of the thrombocytopenia appears to be demonstrated in our case. We observed a marked fall in platelet-count only after clinical relapse with purpuric lesions and a fall in hæmoglobin level.

Symmers (1956) found the histological changes of thrombotic thrombocytopenic purpura before the symptoms had become manifest.

Hinstell and Kligerman (1959) have pointed out the high incidence of a hæmorrhagic diathesis in hyperglobulinæmias of various types. They suggest that some globulins may combine with clotting factors with resultant hæmorrhage. When such combinations dissociate, large amounts of clotting factors are released with consequent clot formation. These workers have demonstrated the combination of globulins with proaccelerin, accelerin, convertin, prothrombin and fibrinogen. This mechanism might play a part in the ætiology of thrombotic thrombocytopenic purpura in cases where hyperglobulinæmia is present.

Summary

In a case of thrombotic thrombocytopenic purpura clinical and hæmatological remission occurred on two occasions after the use of small doses of heparin.

We wish to thank Dr. J. B. Harman for his permission to publish this report and Mrs. M. Moore and the technicians of the hæmatological laboratory.

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"The relationship between Science and Art is similar in function to the very legs we stand and move on. These must be both independent of each other, and, at the same time, harmonious and simultaneous in synchronisation."—Mr. YEHUDI MENUHIN at a meeting of The Royal Institution of Great Britain on Jan. 30, 1959.

Preliminary Communications

HODGKIN'S DISEASE: A MATERNAL-TO-FŒTAL LYMPHOCYTE CHIMÆRA?

THE hypothesis we describe here is based on acquired tolerance, the probable ability of maternal leucocytes to reach the fœtal circulation, and the immunological theory of carcinogenesis

Acquired tolerance is the " outcome of an induced central failure of the mechanism of immunological response brought about by the exposure of animals to antigenic stimuli before the maturation of the faculty of immunological response " [1] That this phenomenon exists has been amply demonstrated [2]

If maternal leucocytes could enter the fœtal circulation by transplacental passage at a time when the fœtus is immunologically tolerant, then these leucocytes could persist and reproduce The lymphocyte is most likely to do this because it has a long life-span [3, 4] and can reproduce [5–8] That maternal red blood-cells may reach the fœtus has been shown by several studies [9, 10] Since the small lymphocyte is of the same order of size as the red blood-cell it should also be able to pass the placental barrier The mature fœtus (adult animal) could then be a lymphocyte chimæra Maternal tumour cells, which are larger than red blood-cells, occasionally pass this barrier [11]

In artificially produced lymphocyte chimæras, tolerance may be one-sided In both radiation chimæras and chimæras produced by injecting newborn tolerant mice with homologous lymphocytes, homologous (" runt ") disease develops [12–14] This is manifested by weight loss, diarrhœa, dermatitis, and a peculiar atrophy and granuloma formation in the spleen and lymphoid organs of the chimærical mice Death finally results Occasionally lymphomas also develop (see below) This reaction occurs only in those animals given homologous lymphocytes or homologous bone-marrow containing lymphocytes Homologous liver cells, or other homologous non-lymphatic tissues, do not cause the reaction Radiation alone or radiation together with injection of isologou lymphocytes does not lead to this reaction Sever workers have suggested that homologous disease resul from sensitisation of the homologous transplante lymphocytes by host antigens, and these lymphocyte then react immunologically against the host [12–15] Per pheral-blood lymphocytes can cause homologous disease [1

An immunological theory of carcinogenesis has bee proposed [17, 18]

Briefly this is that carcinogenic chemicals, viruses, c ionising-radiation agents act by combining with or alterin so-called " identity " proteins or " self-markers " in cells A a result the identity proteins become altered antigenicall This antigenically altered material acts as an autoantigen, an a locally manufactured cellular antibody develops, directe against this now " foreign " material At the same time th agents which caused the antigenic change cause excessiv stimulation and growth in the cells which have had the identity proteins immunologically altered

Thus there exists a selective immune force which will favou the growth of those cells with the fewest identity proteins These cells will survive and proliferate The loss of " identit proteins " constitutes the malignant change, for it is thes identity proteins which, by an interchange between adjacent cells, normally regulate the normal organised relationship between cells [19] It is the same or closely related " self-markers " which permit the recognition of " self " and " not-self " in homografts and autografts [20] Various degrees of tolerance can exist in the mature animal, according to the age of the fœtus at the time of arrival of the maternal lymphocytes In the imperfect partially tolerant lymphocyte chimæra the stage is set for an immunological warfare in which a set of lymphocytes with few or no identity proteins may be selected These lymphocytes are then malignant

We suggest that patients with Hodgkin's disease may be maternal-to-fœtal lymphocytes chimæras of a natural variety—that is, maternal lymphocytes reached them when they were tolerant fœtuses and that the above sequence of events takes place Murine lymphomas have developed in both radiation lymphocyte chimæras [21] and parental-to-F_1 (offspring) non-irradiated lymphocyte chimæras [22]

Since all the transplantation antigens of the skin are also present in the lymphocytes, the chimærical patient with Hodgkin's disease should show some degree of tolerance to maternal skin

METHOD

Five male patients with Hodgkin's disease were homografted with maternal skin The technique was as described previously,[23] except that the split-thickness donor skin was cut

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23 Green, I, Corso, P F *Blood*, 1959, 14, 235

TABLE I—DATA ON 5 CASES OF HODGKIN'S DISEASE IN WHICH HOMOGRAFTS WERE APPLIED

Case no	Age (yr)	Stage *	Duration of disease	Serum-γ-globulin	Recipient type	Donor type	Donor	Survival (days)	Interval between grafts (days)
1	37	III	3½ yr	Normal	A+	A+	Unrelated Mother	18 30	145
2	26	I	6 mos	Slight decrease	B+	B+ O+	Unrelated Mother	14 30	22
3	30	II	1 mo	Normal	B+	B+ O+	Unrelated Mother	140 24	63
4	29	III	1 yr	Slight decrease	A+	O+	Mother	132‡	
5	30	I	10 mos.	Normal	O+		Mother	13	

* A M Jelliffe and A D Thomson, *Brit J Cancer*, 1955, 9, 21 † From time of rejection of first graft. ‡ Patient died with graft intact

TABLE II—TREATMENT

Case no	Radiotherapy			Other			Graft survival	
	Site	Dose (r)	Date	Drug	Dose (mg/kg)	Date	Unrelated	Maternal
1	Neck and mediastinum	3000	June, '54	Mustine	0·4	Sept., '54	Aug 30 to Sept. 16, 57	Feb 11 to March 10, '58
	Lumbosacral area	1650	Jan., '55	Mustine	0·2	June, '55		
	Right lumbosacral	900	April, 56	Mustine	0·4	Aug, '57		
	Left lumbosacral	1200	,, ,,					
	Upper abdomen	900	,, ,,					
	Upper abdomen	1500	Aug ,,					
	Lower abdomen	1500	,, ,,					
	Right jaw	750	Aug 57					
2	Right neck	3000	Jan. 3, 58	None			Jan. 6 to Jan 29, '58	Feb 11 to March 10, 58
			Jan. 28, ,,					
3	Anterior chest	1950	July–Sept., 58				Feb 19 to March 15, '59	July 23 to Dec. 8, '58
	Posterior chest	1950	,, ,,					
	Left supraclavicular	3355	,, ,,					
	Left inguinal	3000	March, '59					
4	Anterior mediastinum	2000	Jan.–Feb, 58	Prednisone		Feb–March, '59		Dec 11, '58, to April 22, '59
	Superior mediastinum	1500	Nov–Dec., 58	'Cytoxan'*	8×6 i.v.	March, 59		
	Retrogastric	1300	Jan., '59	,,	8×5 i.v.	,, ,,		
	Liver	600	Feb–March, '59					
	Right neck	1200	,, ,,					
	Left neck	1200	,, ,,					
5	Anterior chest	1800	Dec., 58–Jan., '59					March 18 to April 1, '59
	Right upper chest and neck	1800	,, ,,					
	Left supraclavicular and neck	1800	,, ,,					
	Left posterior neck	1800						

* Cyclophosphamide.

free-hand from the upper lateral thigh of the maternal donor. The grafts that showed prolonged gross survival were serially biopsied and stained by the Feulgen technique and hæmatoxylin and eosin. The biopsy specimens in case 3 were fixed in 10% formalin and those in case 4 in alcohol formol acetic acid (Davidson's solution).

RESULTS

The gross survival-times of the maternal skin, and the survival-times of unrelated skin grafts previously applied, are shown in table I. The treatment received by these patients is shown in table II, and the proportion of female chromatin marker in biopsy specimens in table III.

Two of the five patients showed prolonged survival of the maternal homografts. In case 3 the Feulgen preparations were of poor quality and the female marker material was present in only 1–3% of cells, but serial biopsies in case 3, stained with hæmatoxylin and eosin, showed decline of the initial inflammatory reaction followed by intense lymphocytic infiltration at the time of gross rejection (140 days), indicating that the original graft was being rejected at this time. In case 4 a high proportion of female chromatin-positive cells in all the biopsy specimens, indicated survival of the maternal graft.

DISCUSSION

Homologous disease and Hodgkin's disease have the following characteristics in common weight loss, skin manifestations, hæmolytic anæmia, and in certain cases unexplained death. Kaplan and Smithers have also noted these similarities.[24]

TABLE III—DURATION OF MATERNAL-SKIN HOMOGRAFTS AND PROPORTION OF FEMALE CHROMATIN MARKER IN BIOPSY SPECIMENS

Case no	Date	Duration of graft (days)	% chromatin-positive
3	July 21, 58	0*	20
	Sept. 8, ,,	49	1
	Oct. 9 ,,	80	Not done
	Dec. 8, ,,	140	3
4	Dec. 11, '58	0*	22
	Dec. 31, ,,	20	20
	Jan 23 59	43	Technically imperfect
	Feb 27, ,,	78	28
	April 13, ,,	123	38
	April 22, ,,	132	43

* Maternal skin obtained at time of homografting the patient.

Unfortunately, the temperature of animals with homologous disease has not been reported. The lymphoid atrophy in homologous disease is often preceded by hyperplasia and granuloma formation with increase in weight of the liver and spleen.[25, 26] The absence of frank homologous disease in the "potential" patient with Hodgkin's disease can be explained by the very large "antigen" excess in relationship to the small amount of postulated homologous lymphoid tissue which is initially present.

The apparently long survival of lymphocytes judged by isotopic marker techniques has been given two interpretations. One is that the lymphocyte itself survives intact for long periods. The other interpretation is that it is not the entire lymphocyte, but only "chunks" of desoxyribonucleic acid (D.N.A.) that survive for a long time, and that these "chunks" of D.N.A. are reutilised to form new lymphocytes. Morphological[27] and theoretical[28] evidence for this last hypothesis has been advanced. If this second interpretation is correct, and if maternal lymphocytes do gain entrance into the fœtus, then the lymphocyte D.N.A. of the fœtus can itself become chimærical, being composed of the D.N.A. of the mother and also of the fœtus.

Some of the murine radiation chimæras developed lymphomas which were composed of the donor-strain lymphocytes.[21] If donor (maternal) lymphocytes could become malignant in patients with Hodgkin's disease, this disease could be treated with polycylic tumour-inhibiting (T.I.) hydrocarbons.[17, 18] These are effective against tumours only where some histocompatibility difference exists between host and tumour. Green has reported preliminary favourable results with T.I. compounds in patients with Hodgkin's disease.[29]

We are well aware of the several possible explanations, besides acquired tolerance, of long-continued survival of maternal skin in patients with Hodgkin's disease. In a previous study, however, in no case of Hodgkin's disease did unrelated skin survive for more than 34 days,[23]

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24 Kaplan, H. S., Smithers, D. W. *Lancet*, 1959, ii, 1.

25 Simonsen, M., Engelbreth-Holm, J., Jensen, E., Poulsen, H. *Ann. N.Y. Acad. Sci.* 1958, 73, 834.

26 Trentin, J. J. Personal communication.

27 Trowell, D. A. *J. biophys. biochem. Cytol.* 1957, 3, 317.

28 Medawar, P. B. *Ann. N.Y. Acad. Sci.* 1957, 68, 255.

29 Green, H. N. *J. chron. Dis.* 1958, 8, 123.

many of these patients were critically ill and had received extensive treatment Many more patients with Hodgkin's disease will have to be grafted, some with maternal skin and some with paternal skin Also, data concerning the survival of maternal-skin homografts in healthy people as well as patients with other chronic illnesses will have to be obtained The validity of the present hypothesis can be investigated in other ways as well We hope that this report will act as a stimulus for further studies

We acknowledge the technical assistance of Miss Nancy Whitehead. We wish to thank Dr H Stambaugh, Dr M Lewin, and Dr M Flynn for performing the skin grafts on these patients, and Dr J Wolf, Dr P Cooper, and Dr T Spaet for their cooperation and support

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SERUM FATTY ACIDS AFTER FATAL HEART-ATTACKS

MANY fatal heart-attacks, while demonstrably due to ischæmic heart-disease, present no recent morbid-anatomical changes in myocardium or arteries to account for the sudden stoppage of the heart's action In a survey in which clinicopathological enzyme tests were used to elucidate the nature of these attacks, blood-lipids were examined also In 50 fatal cases of ischæmic heart-disease and 57 control subjects the simple colorimetric method of Stern and Shapiro[1] has shown serum-fatty-acid levels which may have a bearing on the mechanism of these heart-attacks

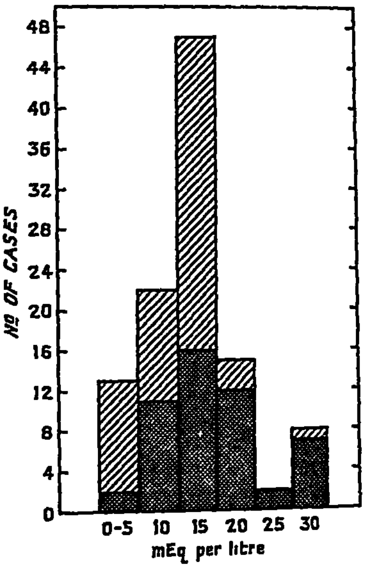
In this series four pathological groups were separated without prejudice to possible interrelationships They are (*a*) simple coronary atherosclerotic narrowing or occlusion, (*b*) fibrosis of the myocardium without recent change or thrombosis of the arteries, (*c*) myocardial necrosis whether or not accompanied by coronary thrombosis, and (*d*) cases in which an arterial thrombus was demonstrated without naked-eye evidence of recent myocardial changes

The mean normal value for serum fatty acids by Stern and Shapiro's method in young healthy adults is about 10 mEq per litre In the four groups described above the mean values were (*a*) 14 2 mEq per litre (27 cases), (*b*) 12 6 mEq (6 cases), (*c*) 15 5 mEq (11 cases), and (*d*) 16 1 mEq (6 cases) The mean value in these 50 cases was 14 7 mEq per litre, whereas the mean for the 57 controls was 9 9 mEq The difference between these means is highly significant ($t=6\ 1$, $p<0\ 001$) The controls were further divided into nine disease groups of which only two were suggestively abnormal, both yielding low values These were the cancer group (10 cases), with a mean of 7 5 mEq per litre, and the group of cardiac deaths not due to coronary-artery disease (12 cases), with a mean of 8 4 mEq

When the distribution of the results is examined (see figure), it is seen that 10 out of 11 values higher than 17 mEq per litre are from cases of cardiac ischæmia The 1 control with a high value was a patient with a pelvic abscess who had died from carbon-monoxide poisoning Furthermore, the values in the cardiac-ischæmia cases show a diphasic distribution whereas the controls are approximately normal in distribution 5 of these 10 high values belonged to the group dying from simple coronary occlusion

The level of serum fatty acids in cadavers is only slightly affected by decay

The mean values in successive 12-hour periods after death were 9 7 mEq per litre (17 samples), 12 2 mEq (35 samples), 12 7 mEq (20 samples), and 15 0 mEq (18 samples) The mean value during the period 4–6 hours after death (5 samples) was 8 8 mEq per litre Thus there was a slow rise starting soon after death These figures exaggerate the rise, since the cancer cases, which had low values, were mostly examined in a hospital mortuary soon after death, while cases of sudden death were examined in the public mortuaries rather later Even so, because the difference in the mean values attributable to differences in the mean time of examination between the deaths from cardiac ischæmia (43 5 hours) and the remainder (37 hours) is only about 0 6 mEq per litre, this cannot account for the significant differences recorded above After 48 hours the mean serum-fatty-acid level fell slightly (10 9 mEq per litre, 13 samples) and after 60 hours it rose again (14 0 mEq , 4 samples) This dip at the end of the accumulation curve is characteristic of several organic substances in cadaver blood, having been seen with hæmoglobin, phenolic substances, and the changes in opacity of deproteinised serum to ultraviolet light[2] In a large series, this reduces further the mean change due to time after death, and therefore undue regard need not be paid to this change



Distribution of serum-fatty-acid values from 107 cadavers

The solid columns represent values from 50 cases of ischæmic heart-disease, and the shaded columns the values from 57 controls

There was no significant difference between the mean ages of the cardiac-ischæmia group (65 years) and the control group (63 years)

The condition commonly recorded on death certificates as " coronary occlusion " is probably a syndrome in which several different factors may be the cause of the fatal insufficiency The high serum-fatty-acid values encountered in this series of cases of ischæmic heart-disease, their similarity to those from cases with recognisable recent organic changes, their dissimilarity from most of the control values, and, particularly, their diphasic distribution suggest that high levels of serum fatty acids may be one of these factors A larger series will enable the effects of selection to be excluded with greater certainty, and it remains to be seen whether any particular fatty acid is regularly responsible for the high values shown by the non-specific colour reaction of Stern and Shapiro's method

This work is supported by a grant from the North East Metropolitan Board research fund

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[1] Stern, I , Shapiro, B *J clin Path* 1953, 6, 158

[2] Enticknap, J B *J forens Med* 1960 (in the press)

Medical Societies

AMERICAN SOCIETY OF HÆMATOLOGY

THE second annual meeting of this society was held in St Louis, Missouri, on Nov 22–24

Antibody Synthesis

Dr HERMAN EISEN (Pennsylvania), who also presented the views of his colleague, Dr FRED KARUSH, said that the two possible modes of antibody formation were the "instructive", requiring the presence of the specific antigen for the formation of specific antibody, and the "selective", which implied the prior existence of specific antibody-forming cells, the "clone" of Macfarlane Burnet. The qualities of a protein molecule, in one or more of which specificity must reside, were aminoacid sequence, helicity, the folding of the helix, and degree of polymerisation There was at present insufficient evidence to indicate which theory was correct and which qualities of a protein antibody conferred specificity

Dr D W TALMAGE (Colorado) inclined to the selection theory, which implied that specific antibody formation was determined spontaneously and that corresponding antigen stimulated synthesis by, and probably reduplication of, the cell carrying this "natural template" Studies of tolerance and immunity suggested, on this theory, that any antigen must have opposite effects on its corresponding clone at different stages of the latter's development

Dr E S LENNOX (University of Illinois) had developed a technique for the determination of antibody production by single cells, using lymph-node cells immunised to various bacteriophages, suspended in droplets, and assaying the power of these cells to inhibit phage activity About 20% of single cells could make two antibodies contemporaneously What appeared morphologically to be lymphocytes were only about half as active in antibody production as what seemed to be plasma cells, but such characterisation was not conclusive, for the cell types might not be stable and in these experiments were not quite "caught in the act" From these findings Dr Lennox argued against the selection theory, though the possibility that a single clone might be capable of producing more than one specific antibody could not be ruled out

Dr A. COONS (Harvard) discussed rate of antibody production in primary and secondary response. Burnet and Fenner had shown that rise in antibody titre in the secondary response was almost logarithmic, and Dr Coons and his colleagues therefore examined lymph-nodes during both types of response, using a fluorescein label to demonstrate the presence of antibody in cells There was scarcely any labelling after primary antigen injection, after a second injection many more cells stained up, though none contained much antibody The positive cells in the node were not clumped in a clone Further experiments were then done to determine whether, in mice, the time between primary and secondary antigen inoculation was directly proportional to the size of the secondary response The secondary response levels off, however, after about 20 days, and Dr Coons speculated that the continuing presence of antigen was required for the clone to continue to multiply At this point discussion arose as to why animals could not be converted almost exclusively into antibody It was assumed that at a critical level further antigen was prevented by antibody already present from exerting a stimulus to further antibody formation

In a comprehensive review of immune tolerance and autoimmune disease Dr R E BILLINGHAM (Pennsylvania) speculated on the late breakdown of immune "tolerance" as a basis for autoimmune disease Normally maintained "physiological quarantine", as in the thyroid, might break down, or late maturation, as in the breast or testis, might occur, so that tolerance might not have been acquired, or perhaps some lymph tissue might exist in a state of "quarantine", possibly in the thymus, and constitute a threat to earlier acquired tolerance In comparing the ability of cells of various origins to produce "tolerance" on the one hand, and "runt disease" on the other, Dr Billingham stressed that both the type of cell and the numbers in the inoculum were important Lymphocytes seemed to be effective in producing both phenomena, but thymus cells might produce "runt disease" but not "tolerance"

Ætiology of Leukæmia

Dr JOSEPH BEARD (Duke) followed his own aphorism that "people get up to talk about human leukæmia and the first thing you know they're talking about mouse or chicken leukæmia" He had found what he felt must be virus particles in thin sections of blast cells in acute human leukæmia observed with the electron microscope in only 1 case in 12, whereas Dmochowski in Houston had 50% positives In fowl leukæmia, however, no virus particles were seen either, unless the blast cells were grown in culture, when they became loaded Dr LUDWIG GROSS (New York) pointed out that virus might not always show up under the electron microscope and what did show up might not be virus Dr S SCHWARTZ (Chicago) developed his theme that variations in incidence of induction of leukæmia, using material from patients with leukæmia, might be due to different balance between virus and inactivating factors

Radiation as a factor was discussed by Dr EUGENE CRONKITE (Brookhaven) He presented arguments against interpreting any data at present available as showing that irradiation was leukæmogenic He seemed not to be wholly convinced by his arguments himself, and finally agreed that at present a policy of playing safe was probably the best working basis

Dr ROBERT HEYSSEL (U S Public Health) presented the most recent figures for the incidence of leukæmia in the Japanese atom-bomb areas The errors in assessing dosage of radiation were recognised as being very great, and there was clearly much divergence of opinion about the significance of conclusions which have been drawn from earlier figures

Dr GEORGE WOOLEY (Sloan-Kettering Institute) summarised what is known about chemical and hormonal factors in leukæmogenesis in animals, emphasising the importance of the thymus for induction of leukæmias and tumours, and mentioning Metcalf's claim that a lymphocyte-stimulating factor (L S F) was found in plasma of mice which later developed lymphoma Dr J TRENTIN (Houston) mentioned that rises in L S F had been observed after irradiation and he postulated that L S F could be the mediating agent for leukæmia.

The epidemiology of human leukæmia was then briefly discussed, and the point was the need for good studies in this field At this stage the chairman, Dr JACOB FURTH (Roswell Park), took a show of hands of those who believed that a virus, radiation, hormonal and chemical factors, or genetic factors had been a causative factor in any one of their cases of leukæmia Of a total of about 600, 26 raised their hands for radiation, 15 each for chemical and genetic causation, and viruses came a poor fourth

Notable among other contributions was a group of observations on transformation of human leucocytes into histiocytes, fibroblasts, and fat cells in subcutaneous diffusion chambers made of 'Micropore' Dr N L PETRAKIS (San Francisco) showed pictures of his preparations, with collagen fibres forming in chambers in which only cells from the buffy coat had been placed

Dr E DONNALL THOMAS' group (Cooperstown) had been studying hæmoglobin synthesis in fœtal tissues It seems that adult hæmoglobin is formed from the earliest period (about 9 weeks) onwards and that all organs producing hæmoglobin produce both the adult and fœtal type in proportions constant for the particular tissue

Dr S PIOMELLI (Boston), in studying "secondary disease" in X-irradiated rabbits, transfused with homologous bone-marrow, found that transfusion immediately after irradiation was life-preserving, 12 hours later it was ineffective Incomplete red-cell antibodies were found in the serum of the runts so produced, with a positive Coombs test 3–7 weeks later Red-cell survival in these animals was always reduced but full-blown secondary disease was rare and less severe than in rodents Since rabbits are not pure-bred these results were considered encouraging Dr W HOLLANDER (Oak Ridge) pointed out that mice with spleen-induced "runt disease" have a leucopenia but not a positive Coombs test

Dr W DAMESHEK (Boston) and his colleagues presented data showing that so far no success has been obtained in the treatment of aplastic anæmia with bone-marrow transfusions

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Reviews of Books

Medical Surveys and Clinical Trials

Editor L J WITTS, C B E, M A, M D, SC D, F R C P, Nuffield professor of clinical medicine, University of Oxford London Oxford University Press 1959 Pp 328 35*s*

Professor Witts has collected the experience and outlook of many experts on population surveys, follow-up studies, and therapeutic trials His co-authors are all well known and their contributions are of great interest All who wish to undertake such large investigations should consult this book, which indicates both the value and the difficulties of population surveys The widespread and proper use of statistical method, so desirable, is not always easy to achieve, and often enormous numbers of subjects have to be studied before an answer becomes clear Almost everyone has been impressed by the statistical evidence which proved the value of streptomycin in pulmonary tuberculosis, which linked cancer of the lung with cigarettes, and maternal rubella with fœtal abnormalities but these were all elaborations following strong clues from previous clinical observation and experience A well-known survey of blood-pressure in a population led to much controversy and revealed the difficulties of tackling a problem by survey methods alone The question seems to have been clarified by the application of knowledge based on extensive clinical and pathological experience, and once again the professional habit of dividing normal from abnormal systolic blood-pressure at about 160 mm. Hg appears to be reasonable In short, the statistical approach may be quite unintentionally confounding unless regulated by strict attention to the existing body of knowledge Even "high statistical significance" is not proof, unless the idea finds other scientific support

The survey method is often extremely costly from its very magnitude, and sometimes the problems posed are capable of solution by precise laboratory methods on much smaller numbers The open mind free from bias, beloved of the statistician, can conceal medical amateurishness or even ignorance, while the good clinician is discouraged from detailed observation and questioning by the requirements of "double-blind" trials Subjective judgments inevitably come in, and in one blood-pressure survey in Bergen there was an obvious inclination to record the pressures in the nearest round figure Observer error in all clinical matters is a well-recognised phenomenon, and if we could believe all that has been written about it, it is amazing that diagnosis is as satisfactory as it seems to be in practice In large population surveys complete individual case analysis is impossible and records are often made of some single measurement or parameter If our predecessors of the year 1800 had surveyed "anæmia" based on hæmoglobin only, what light would have been cast on blood disorders? More recent attempts to define a mutation-rate in hæmophilia become of little value as we realise the number of concealed cases with only slight reduction of antihæmophilic globulin Thus the modern view drives us back to the laboratory work of the scientists for inspiration and guidance Without the backing of a well-founded idea, surveys are apt to be sterile, and the best statisticians cannot extract the answers

One or two of the contributors to this monograph pay little attention to the laboratory approach the editor himself says "the location of clinical scientists in hospitals invites the danger of an increasing impoverishment of ideas much current research is trivial in conception" This is a challenge which many will find provocative All who are interested in surveys and particularly those who imagine they are easy ways to dramatic conclusions should read this book and take warning

Aldosterone in Clinical and Experimental Medicine

E J ROSS, M D, PH D, M R C P, senior lecturer in medicine, University College Hospital Medical School, London Oxford Blackwell Scientific Publications 1959 Pp 144 22*s* 6*d*

ALDOSTERONE was discovered only five years ago and is still, and likely to remain for some time, the focus of much research It has attracted interest in many countries because its role in controlling electrolyte metabolism is of concern to biochemists, physiologists, and clinicians Dr Ross, who has worked in Dr George Thorn's laboratories at the Peter Bent Brigham Hospital in Boston, is in a strong position to discuss aldosterone from every possible aspect, and he does so very ably in this concise monograph

From a basis of 539 references he discusses all that is known about the hormone, and he has done a great service to all kinds of workers in this field by his review of the extensive literature. He writes clearly and factually, and it is not until the last chapter, on the role of aldosterone in human homœostasis, that he allows any speculation Dr Ross is not afraid to say what is not known and to point the way for future research

This book is an excellent summary of the position at half-time We hope Dr Ross will be able to report the outcome of the game when the final whistle is blown

The Principles of Humane Experimental Technique

W M S RUSSELL, M A, D PHIL, UFAW research fellow, department of zoology and comparative anatomy, University College London, R L BURCH, hon UFAW research assistant London Methuen 1959 Pp 253 30*s*

THE object of this book, sponsored by the Universities Federation for Animal Welfare, is to ensure that experiments on animals involve the least possible inconvenience to them, while increasing the scientific value and reliability of those experiments which are performed

The authors summarise the matters to which they draw attention as follows (1) belated knowledge of the relative numbers of species used, (2) persistent use of the Friedman test, (3) delay in the initiation of microbioassay, (4) delay in the exploitation of statistical methods, (5) delay in the rationalisation of breeding methods for uniformity, (6) delay in noticing published effects of environmental factors, (7) delay in the application of psychosomatic principles, (8) conservatism in the choice of laboratory species, and (9) the guarded approach to several aspects of toxicity testing These are all questions of moment to the research-worker, who, however, it should be said in justice to him, recognises them all

The authors have presented their work as if it were a review article, and have copiously burdened the text with references, most of which are not likely to be challenged by the reader of a book of this type For this reason it may fail to reach the audience to which it is directed Its purpose is admirable, and its matter unexceptionable But it is not easy reading a shorter and more dogmatic paper would have made a stronger impact, and lost none of its authority

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Pharmacopœa Internationalis (*Supplement* Geneva World Health Organisation 1959 Pp 224 25*s* Obtainable from H M Stationery Office, P O Box 569, London, S E 1) — The first edition of the *International Pharmacopœa*, volumes I and II of which appeared in 1951 and 1955, is completed by this supplement containing a further 94 monographs and 17 appendices

THE LANCET

LONDON 2 JANUARY 1960

Into the '60s

> " He who plays a part in events is the last to know their real importance, and the moment he tries to seize their purport, and to take a conscious part in them, his actions are barren of result."

Describing the situation after the fall of Moscow in 1812, TOLSTOI wrote of the uselessness of people who tried to understand what was going on, compared to the usefulness of the army, which did not trouble its head with large affairs but continued to think about " the next quarter's pay, the next halting-stage, of Matrechka, the vivandiere, and so forth "[1] Similarly in Medicine one may argue that the only useful thing is to get on with the job—with the good work that will make all the difference to some individual patient or (if an investigator has luck or genius) may transform the outlook for thousands or millions, as happened through the discovery of penicillin and streptomycin.

But TOLSTOI overstated his case. Few armies remain long in the field unless there is at least enough intelligent planning to ensure that they receive their pay, their food, and their ammunition, and few armies win battles unless arrangements are made for them to be in the same tract of country as the enemy. In the war on disease the same is broadly true, and, because this war becomes steadily more elaborate, we cannot avoid more organisation of one sort or another. We all know, of course, that what ultimately matters in Medicine is the care of the patient and the prevention of disease, but the kind of organisation matters greatly, too, because a defective one will not supply the medical troops with what they need and will not deploy them where they are wanted most. In this country our biggest attempt at medical organisation—the National Health Service—has not proved nearly so restrictive as many of us feared, but it is not yet as constructive as some of us hoped. it has preserved most of what we valued but it has failed to add what we might value more. On the performance of its difficult first decade, the mark it deserves is perhaps an Oxford β (opinion will differ on whether a β— or a β—), and the question to be decided in the '60s is whether the burden of routine will keep it at this merely respectable standard or whether it will achieve the α of which it is capable. To do so it needs, of course, more money, but it also needs more of the rare kind of discontent that gets things done. In the '60s scientific Medicine is likely to accelerate its startling progress, and at all levels we shall need corresponding flexibility and enterprise. Considering the difficulties, our service is good and economical, but the public will still have bought it too dear if, under Government auspices, it loses the adaptability which is a sine-qua-non for biological success in a changing environment.

Some of our present problems are those of the particular kind of organisation we have created. For example, something will sooner or later have to be done to make the Ministry of Health less like an ordinary Government department and more like the nerve-centre of a complex public and professional service. (The Government so far show no sign of having read the Acton Society and Sir GEORGE SCHUSTER[2] on this far from negligible subject.) Something will have to be done, too, to bring the English regional hospitals and the teaching hospitals more closely together, in the interest of both. (Probably the time has come to begin an inquiry into the size of the regions, the function of regional boards and hospital management committees, and the simplification of their administrative machinery[3].) Again, something will have to be done about remuneration in the health service—" the next quarter's pay "—on which the Royal Commission should be reporting at the end of February. But beyond such local and relatively soluble problems are more universal and intractable ones arising mainly from the rapid industrialisation of medical work. For instance, even in the prosperous United States, a great many hospitals find it as hard as many of ours to maintain a proper junior staff. Far more important, the future of personal medical care remains uncertain everywhere except in those Communist countries where the general practitioner has been frankly abolished in favour of the small specialist team. Scarcely anywhere, as yet, does the prevention of disease get as much attention as its treatment. And in Medicine, as in international relations, there is an ever-increasing risk that uncontrolled science will neutralise humanity.

In the past decade we in this country have been making the overdue transition from a commercial type of medical practice to one in which the patient's needs can be considered first, last, and all the time. That in itself is an achievement, and one in line with professional tradition. Furthermore, whatever we may feel about our national deficiencies, monetary or mental, we still have in Britain an exceptionally favourable environment for practising and improving and enriching medicine. Our country is geographically small but intellectually extensive, and its political stability is such that it can accept considerable changes without disruption. Unhappily, with that innate respect for the past which the past, as a whole, so seldom deserves, many members of our profession, both old and young, are inclined to underestimate the current British contribution to Medicine. The truth, however, is that though there are some things we cannot do, there are many—both scientific and social—which we do better than anybody else. From those individual pursuits and personal preoccupations which TOLSTOI commended we can still confidently count on our quota of discoveries—usually no more than tiny points of light but just occasionally some great flash And likewise from a certain national ingenuity in that art of organisation which TOLSTOI was inclined to underrate, the public can expect further benefit because good organisation promotes good use of new knowledge

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[1] War and Peace. Everyman's Library edition, vol iii, p 176. London, 1917.

[2] See *Lancet*, 1959, i, 349.

[3] *ibid* 1958, ii, 27.

If one may judge by what happened in the first six decades of this century, nobody need fear lack of incident or interest in the seventh Least of all, perhaps, anybody with insight into diseases and health, and a liking for the people who have them

Genesis of Cardiovascular Murmurs

THE presence of a murmur does not depend on any vital property of the heart or blood-vessels Its primary cause is an alteration in the nature of flow of the blood itself, the solid structures forming the boundaries of the fluid are thrown secondarily into a state of greater or lesser vibration These conclusions, set out by CORRIGAN[1] for these columns some years ago, have not been seriously challenged

CORRIGAN pointed out three anatomical conditions which tend to give rise to murmurs constriction of the lumen of a vessel, a constricted orifice leading to a normal cardiac chamber or vessel, and a normal orifice opening into a dilated chamber or vessel For such murmurs, and for the murmurs of high-output states and those accompanying abnormal anatomical communications, the altered character of flow may be turbulent[2] (fluid particles moving at random), more or less orderly with the production of eddies (vortices),[3] or associated with a periodic vortex-ring pattern[4] (musical jet) or with the formation and collapse of bubbles of dissolved gas or of water vapour (cavitation)[2]

In a long uniform cylindrical tube, turbulence develops in a homogeneous fluid flowing at a constant rate when the Reynolds number VD/ν (velocity × diameter/kinematic viscosity) exceeds 1900[2] The corresponding critical Reynolds number for blood is 1940±160[5] REYNOLDS[6] noted that with varying flow, and with steady flow in a channel which converges or diverges or which has a rough wall or non-circular section, the critical velocity associated with the onset of turbulence is not necessarily determined by this function VD/ν McDONALD[7] doubts whether turbulence is as important a source of murmurs in the cardiovascular system as was once held, and now BRUNS[8] has expressed the view that the acoustic energy generated by turbulence is inadequate to account for audible murmurs Although he describes various ideas in support of this view, the evidence—particularly on the interaction between a turbulent fluid boundary layer and a vessel or cardiac wall—must be regarded as incomplete

The existence of eddies or vortices (generated, for example, by an obstruction in the path of flow) may be causally related to murmurs[7] since a considerable pressure drop may exist in their centres BRUNS[8] discusses the analogous phenomenon of Æolian tones[9] [10] (a familiar example of which is the singing of wires in a wind), and the associated rhythmic shedding of eddies[11] which stem from a cylindrical wire placed in the path of a constant flow of air These have been studied extensively[12–15] Such eddies in a fluid medium consist of localised spinning masses of fluid, these pass downstream for some distance before dispersing The rate of development of eddies is more or less regular, and since this generation occurs alternately from each side of the obstacle, two rows of vortices are formed downstream Sound is emitted from such a wake, and the frequency or pitch of the tone corresponds to the rate of shedding of vortices[3] This frequency is proportional to the ratio of the fluid velocity to the diameter of the cylindrical wire[10] Slight irregularities of form of the cylindrical wire give rise to a frequency spectrum of sound—i e, noise[8] BRUNS draws attention to the movement of the bulk of fluid comprising the wake, rather than the vortices themselves, as the source of acoustic power Similar sounds have been noted from the wakes generated by vanes in flowing water[16]

The rhythmic disturbance of an axially symmetrical jet, associated with the formation of ring-vortices,[17] is a related phenomenon[18–20] SAVART[20] in 1854 described a loud tone heard when a jet of water issues from a small orifice into air or water The frequency of generation of ring-vortices from such an orifice is related to the velocity in a somewhat stepwise fashion,[20] or, more generally, to the Reynolds number,[21] and tends to increase with increasing velocity or diminishing jet diameter The same vortex pattern develops for larger orifices, even those almost filling the lumen of a vessel[8]

Considerations of acoustic energy,[7] [8] of the frequency, intensity, and transmission of particular cardiovascular murmurs,[8] and of KÁRMÁN's classical theory[12] [22] of "vortex streets" point to the importance of such eddies in the production of murmurs. The low pitch of downstream-propagated murmurs (of mitral stenosis and aortic stenosis, for example) and the higher pitch of upstream-propagated murmurs (of mitral insufficiency) are compatible with this concept[8] The model experiments of BRUNS are in some respects confirmatory, for example, the intensity of low-frequency components of the murmur generated by a constriction in a vessel increases at first as the stenosis is made smaller, but for very small orifices the intensity falls off again, as predicted by BRUNS on the basis of vortex theory

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1 Corrigan, D J *Lancet*, 1829, ii, 33
2 Reynolds, O *Phil Trans A*, 1883, 174, 935
3 Relf, E F, Ower, E Aeronautical Research Committee Reports and Memoranda 1921, no 825
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5 Coulter, N A, Jr, Pappenheimer, J R *Amer J Physiol* 1949, 159, 401
6 Reynolds, O Papers on Mechanical and Physical Subjects, vol 2 Cambridge, 1901
7 McDonald, D A *Circulation*, 1957, 16, 270
8 Bruns, D L *Amer J Med* 1959, 27, 360
9 McKusick, V A Cardiovascular Sound in Health and Disease Baltimore, 1958
10 Anderson, A B C *J acoust Soc Amer* 1955, 27, 13
11 Mallock, A *Proc roy Soc* A, 1907, 79, 262
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15 Yudin, E Y National Advisory Committee for Aeronautics, tech memo 1947, no 1136
16 Gongwer, C A *J appl Mech* 1952, 19, 432
17 Strouhal, V *Ann Phys Chem* 1878, 5, 216
18 Johansen, F C *Proc roy Soc* A 1929, 126, 231
19 Birkhoff, G, Zarantonello, E H Jets, Wakes and Cavities New York, 1957
20 Savart, F *Phil Mag* 1854, 7, 186
21 Anderson, A B C *J acoust Soc Amer* 1955, 27, 1048
22 Spitzbarth, von H, Weyland, H, Gersmeyer, E F *Z Kreisl Forsch* 1958, 47, 965

Euler[23] foreshadowed the importance of cavitation in hydraulics in 1754 Reynolds cavitation [6 24 25] associated with fluid flow through a constriction is unlikely to be a common source of significant cardiovascular sound since the pressure differential required across the stenosis (about 350 mm Hg) is rarely achieved)[8] Gas-entrained bubbles would emit frequencies above the important components of most murmurs[26] Nevertheless, the possible existence of a different form of cavitation[7] associated with the low pressures at the centres of vortices cannot be disregarded

The clinical importance of understanding the mechanism of genesis of murmurs was recognised by **Corrigan** Clearly the story is not yet complete Meanwhile we should recognise the fallacy of simply equating turbulence with murmur production, the need for considering further the consequences of the pulsatile character of flow, and the interplay between the primary disturbance in the blood and the secondary disturbance of the boundaries

A New Familial Abnormality of Red Blood-cells

In the past few years information has been accumulating about an entirely new type of intrinsic abnormality of red blood-cells—an enzyme deficiency which is usually harmless unless the cells are exposed to one of several drugs or ingested substances[27] The existence of this defect was discovered during an investigation of the acute hæmolytic anæmia caused by primaquine—an 8-aminoquinoline drug, chemically similar to pamaquin, used for the treatment of malaria Cases of this anæmia caused by pamaquin had been described by **Manson-Bahr**[28] in 1927, by **Cordes**[29] in 1928, and by many others later The patients were extensively investigated by current techniques, but the results were negative no constant immunological abnormalities were detected, there was no abnormality of red-cell fragility and no sickling, and there was no correlation between the plasma level of pamaquin or primaquine and the degree of hæmolysis But there were some positive observations In a sensitive patient primaquine always induced hæmolysis except for a time after a dose, during which further doses did not cause hæmolysis Primaquine sensitivity is not common, but it is relatively more frequent among Negroes, and British troops have been observed to be less susceptible than Indians or Burmese The clinical course of the hæmolytic reaction is very characteristic In a susceptible person no evidence of hæmolysis appears for the first two to three days, and this latent period occurs whether primaquine is being given for the first or a subsequent time The signs include hæmoglobinuria, icterus, and a rapid decrease in red cells and hæmoglobin, reticulocytosis develops and **Beutler** et al[30] pointed out that Heinz bodies appear in many of the red cells The Coombs reaction for adsorbed antibodies remains negative The acute phase lasts about a week, and recovery ensues, even if the administration of primaquine is continued This apparent tolerance lasts for a few weeks after withdrawal of the drug, and another dose then produces exactly the same sequence of symptoms and signs **Beutler**[27] notes that some other drugs such as acetanilide, sulphanilamide, and nitrofurantoin cause a similar clinical picture of hæmolytic anæmia in susceptible patients

Such a drug-induced hæmolytic anæmia could be due either to the production in the blood of abnormal factors that affected red cells, or to some abnormality of the red cell itself In 1954 **Dern** et al[31] showed that sensitivity to primaquine was due to an intrinsic abnormality of the red blood-cells Red cells from a sensitive person were labelled with radio-chromium and infused into a non-sensitive person, primaquine (30 mg daily) was given to this non-sensitive recipient, and the labelled red cells were rapidly and selectively destroyed Conversely labelled red cells from a non-sensitive person transferred into a sensitive patient were unaffected by administration of primaquine The primaquine-sensitive cells were fully investigated by **Beutler**, **Dern**, and their co-workers None of the previously known red-cell abnormalities were present, and eventually investigation of the Heinz bodies provided the clue When sensitive red cells were incubated in the presence of oxygen with certain reducing substances, such as acetylphenylhydrazine and ascorbic acid, they developed a pattern of Heinz bodies—denatured protein particles—which was consistently different from that appearing in non-sensitive cells[32] **Beutler** et al described a test for detecting sensitive cells heparinised blood is incubated for four hours with a pH 7 6 phosphate buffer, containing 200 mg glucose per 100 ml and 100 mg acetylphenylhydrazine per 100 ml , wet preparations are stained with crystal-violet and observed under the microscope In a sensitive person more than 40% of the cells contain 5 or more Heinz bodies, whereas in almost all non-sensitive persons less than 30% of the red cells contain this number These findings have been confirmed by others and noted in some other drug sensitivities, and **Larizza** et al[33] found the same sensitivity in the red cells of patients with favism—the curious hæmolytic anæmia, well known in Sardinia and southern Italy, that develops in some who eat broad beans (*Vicia fava*) or are exposed to the pollen of the broad-bean flowers

The next step was the demonstration by **Beutler** et al[34] that the glutathione content of sensitive red cells tended to be below normal and that poisoning of non-sensitive cells with iodoacetate, which binds sulphydryl groups, caused them to react like sensitive cells in the Heinz-body test Later these workers found that when red cells from primaquine-sensitive patients were incubated for two hours with acetylphenylhydrazine the glutathione content fell sharply from a starting level of about 50–70 mg per 100 ml of red cells to less than 12 mg per 100 ml , whereas with cells from non-sensitive persons with a normal starting level of 50–80 mg per 100 ml the figure remained above 44 mg per 100 ml This observation has been developed into a " glutathione-stability test " by means of which red blood-cells affected by this abnormality can be readily detected [35] The glutathione content of red cells was determined by a modification of the colorimetric technique of Grunert and Phillips [36] based on the development of a rose-coloured complex with sodium nitroprusside and its stabilisation with cyanide The reason for this instability of glutathione is thought to be an enzyme deficiency, Beutler et al [37] have carried out experiments that suggest that there is a deficiency of glucose-6-phosphate dehydrogenase, but other enzymes concerned with carbohydrate metabolism in the red cells may also be involved

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[23] Euler, L Cited by V A McKusick and H K Wiskind (footnote 24)

[24] McKusick, V A , Wiskind, H K *Bull Hist Med* 1959, 33, 116

[25] Strasberg M *J acoust Soc Amer* 1956, 28, 20

[26] Wiskind, H K *Circulation*, 1957, 16, 270

[27] Beutler E *Blood*, 1959, 14 103

[28] Manson Bahr, P *Proc R Soc Med* 1927, 20, 925

[29] Cordes, W *Arch Schiffs- u Tropenhyg* 1928 32, 143

[30] Beutler, E , Dern, R J , Alving, A S *J Lab clin Med* 1954, 44, 177

[31] Dern, R J , Weinstein, I M , LeRoy, G V , Talmage, D W , Alving, A S *ibid* 1954, 43, 303

[32] Beutler, E , Dern, R J Alving, A S *ibid* 1955, 45, 40

[33] Larizza, P , Brunetti, P , Grignani, F , Ventura, S *Hæmatologica*, 1958, 43, 205

[34] Beutler, E , Dern R J , Flanagan, C L , Alving, A S *J Lab clin Med* 1955, 45, 286

The glutathione-stability test has been tried in many blood diseases, and in most the results are negative Positive results are, so far, limited to the hæmolytic anæmia induced by certain drugs in sensitive individuals and in favism The results with favism are of much interest, since it is known to be an inherited disease Sansone and Segni [38] and Larizza et al [33] in Italy and Szeinberg et al [39] in Israel found that the cells in patients with favism showed glutathione abnormalities like those in primaquine-sensitive patients Sansone and Segni eventually found that in patients with favism the red cells gave positive results with the Heinz-body test and the glutathione-instability test of Beutler, and they showed a deficiency (often complete) of glucose-6-phosphate dehydrogenase These workers and others since have detected this enzyme abnormality of the red cells in apparently unaffected relatives of patients with favism, and the defect was shown to be less complete in females than males Sansone concluded that the defect was inherited as a dominant partially sex-linked character Childs et al,[40] in Baltimore, have carried out an extensive genetic study of the probably identical primaquine-sensitivity of red cells

They selected Negroes for this study since the defect is known to be commoner among them than among the white population, and they used the glutathione-stability test for sorting In a group of 144 Negro males and 184 Negro females, the prevalence of sensitive individuals, or " reactors ", was found to be about 14% in males and 2% in females, but in addition 5% of females showed partial or " intermediate " sensitivity Reactors were found in 16 families, and all cooperative members of these families were tested—90 females and 73 males The results showed again a preponderance of reactor males, but female reactors and intermediates together almost equalled the males Affected members were found in an many as three generations In family 1, for example, a female reactor was found in generation 1, but her husband was not tested, of her 5 children, 1 male and 1 female were reactors, the male married a normal female and had a normal son and a reactor daughter, this daughter married a normal male and had 4 daughters of whom 3 were intermediate reactors, 1 of these has married a normal male and had 6 children, all normal, in addition 1 of the apparently unaffected females of the second generation married a normal male and had an intermediate reactor daughter

Childs et al suggest that the most likely mode of inheritance is " sex-linkage with incomplete dominance ", thus agreeing with the results from favism

Possibly other so far unexplained hereditary hæmolytic disorders may prove to be due to enzyme defects rather than to allergy or undefined immunological abnormalities Thus at the recent European conference in London Dr. T A J Prankerd pointed out that an abnormality of glycolysis has been detected in the red blood-cells in hereditary spherocytosis, and a defect of phosphoglyceromutase has been found in the red cells of a family with the congenital non-spherocytic hæmolytic anæmia described by Crosby [41] Such investigations are so far in the early stages But the Heinz-body test is easy to carry out, and the glutathione-stability test is feasible in any biochemical laboratory, and these tests should clearly be applied in patients with drug-induced hæmolytic anæmia or unidentified hæmolytic anæmia The workers who began to investigate once again the oddities of the hæmolytic anæmia induced by primaquine can hardly have anticipated that they would end by providing an explanation of favism There are still many curious facts to be explained about these anæmias, but these researches have notably advanced our understanding of them

Dental Drills

The earliest dental drills were based on either the jeweller's bow drill or else the Archimedean drill, which resembled those used in fretwork The first power-driven drill was invented by G F Harrington, who in 1864 patented a clockwork device which would run for two minutes on one winding [42] The treadle-driven foot engine was introduced by Morrison in 1870–71 An electrically driven drill had been invented by G F Green in the 1850s [43], but this seems to have been little used In 1868 Green introduced a pneumatic engine in which the drill was " propelled by a certain mechanism " contained in the handpiece The first practical electric engine is supposed to have been made by the firm of Siemens-Schuckert, but the foot engine continued in use well into the 1920s

Nearly forty years ago it was decided on theoretical grounds that the optimum cutting speed was in the neighbourhood of 300,000 revolutions per minute (r p m) for a 1 mm ($^1/_{25}$ in) diameter bur or carborundum point, but no apparatus operated at such a speed, which is the equivalent of a linear speed of 12–15 metres (37–46 feet) per second Until about 1943, when diamond cutting instruments were introduced, the maximum speed of most dental engines was about 4000 r p m Tungsten-carbide burs came into production soon afterwards, and they, too, were found to cut better at higher speeds WALSH and SYMMONS[44] reported that high rotational speeds reduced unpleasant vibration, and this observation was confirmed by INGRAHAM and TANNER,[45] who also noticed that tension, and consequently fatigue, for both operator and patient diminished at speeds over 6000 r p.m WALSH and SYMMONS[46] found that the most unpleasant vibrations were those generated at rotational speeds between 6600 and 9500 r p m There is little advantage in increasing speeds from 26,000 to 45,000 r p m , but at speeds from 45,000 to 100,000 r p m there is a spectacular increase in cutting efficiency, which becomes twenty to thirty times that at 4000 r p m[47] The cutting rate of an ordinary steel bur continues to increase with speeds up to 10,000 r p m or thereabouts, diamond instruments perform best at 60,000–80,000 r p m , while the cutting power of tungsten-carbide burs continues to increase with speed up to the maximum at present obtainable In 1953 NELSEN et al[48] described a 61,000 r p m hydraulic turbine handpiece, and two years later MCEWEN[49] described a belt-driven handpiece which attained a rotational speed of 200,000 r p m , at this speed the vibration frequencies were beyond the threshold of perception, and the cutting efficiency was far greater than any previously attained Air-turbine instruments were developed in 1956, these operate at rotational speeds of 200,000–300,000 r p m, and use small-diameter diamond or tungsten-carbide cutting tools Cavity preparation by a carbon-dioxide-propelled jet of aluminium oxide ("airbrasive" technique) and ultrasonic vibratory drills have been tried, but neither method has become popular

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[35] Beutler, E , Dern, R J , Flanagan, C L , Alving, A S *ibid* 1957, 49, 84
[36] Grunert, R R , Phillips, P H *Arch Biochem* 1951, 30, 217
[37] Beutler, E , Robson, M , Buttenweiser, E *J clin Invest* 1957, 36, 617
[38] Sansone, G , Segni, G *Boll Soc ital Biol sper* 1956, 32, 456, ibid 1958, 35, 327
[39] Szeinberg, A , Sheba, C , Hirshorn, N , Bodonyi, E *Blood*, 1957, 12, 603
[40] Childs B , Zinkham, W , Browne, E A , Kimbro, E L , Torbert, J V *Bull Johns Hopk Hosp* 1958, 102, 21
[41] Crosby, W H *Blood*, 1950 5, 233
[42] Lufkin, A W A History of Dentistry , p 275 London, 1949
[43] Taylor, J A A History of Dentistry , p 135 Philadelphia, 1922

At high speeds, because only a light touch is needed to guide the bur, fatigue in the operator is lessened, and, with the almost fortyfold reduction in the amplitude of vibrations transmitted to the tooth, the whole procedure is much less trying for the patient. This in itself encourages better dentistry, and often a great deal more can be done without recourse to local analgesia High-speed cutting, though more painful than the abrasive jet, which is the best-tolerated method of all, is nevertheless far more acceptable to the patient than conventional speeds[50] But what of the risks? The dental pulp may be injured during the preparation of the smallest cavity because of its susceptibility to both thermal and pressure changes Fortunately this damage is usually only temporary, but the higher the cutting speed and the deeper the cavity, the more lasting is it likely to be Since the introduction of "threshold" high speeds[50] (10,000–18,000 r p m) it has become usual to cool the tooth with either a jet or a spray of water during cutting The importance of adequate cooling has been shown by VALE,[51] who measured the temperature rise in the pulp chamber of an extracted tooth Using a diamond instrument at 3500 r p m, the temperature in the pulp chamber rose to 21°C above ambient, with water cooling, the rise was only 4°C A tungsten-carbide bur rotating at 17,000 r p m caused a temperature rise of 40°C, whereas with spray cooling it was only 9°C An air turbine with a diamond instrument, using air cooling alone, produced a temperature rise of 16°C, compared with zero when a water jet was used Some operators (and patients) have remarked on a smell of burning which often accompanies cutting in some instances incandescence of the enamel has been noted Whether this is just a surface effect, as is suggested by measurements of pulp-chamber temperature, or whether enough heat is generated to injure the pulp is uncertain, but a sandpaper disc rotating at 4000–5000 r p m. can produce the same smell without any complaint from the patient Air turbines are not suitable for use with large-diameter cutting instruments—the linear speed of a cutting particle on a disc is too high, and the torque of the turbine too low Damage to the cells of the pulp[51] is a disturbing feature of high-speed cutting Cell disorganisation is known to develop at frequencies in the neighbourhood of 1 5 megacycles (10^6 cycles) a second, and possibly an air turbine running at 250,000 r p m could generate harmonics at this frequency Further research is needed into this point, and into the occasional disintegration of large portions of enamel probably this is due to microscopic flaws in the enamel, or else to the tooth coming into resonance with the natural frequency of the cutting instrument or some harmonic of it

Even its most enthusiastic advocates cannot deny that the air turbine is noisy, and that its high-pitched whine carries some distance. Surprisingly, the patient is usually the last person to complain of this[50], airborne noises apparently cause less distress than those conducted through bone KILPATRICK[50] suggests that the surgery be lined with acoustic tiles, and music played through insert-type earphones to soothe the patient GARDNER and LICKLIDER[52] have recommended the use, besides music, of a random noise, consisting of a strong, low-frequency component combined with a weaker and higher-frequency one Fear has been expressed that continual exposure to the high-pitched note of the air turbine may injure the ears of the operator—though no such injury has yet been observed One manufacturer has reduced the noise by returning most of the exhaust air to the cabinet of the machine Because of the high frequencies involved, a very small built-in silencer near the rotor of the turbine should eliminate much of the more unpleasant noise, but this does not seem to have been tried The small ball races in the handpiece contribute a fair amount of mechanical noise, and silencing these presents greater difficulties Disquiet has also been felt at the force with which particles of tooth substance and pieces of old filling material are propelled into the air by the blast of the turbine exhaust For the patient this is unlikely to be a serious hazard, but the operator might be well advised to wear some form of mask An aspirator, more efficient than the usual water-operated saliva ejector, is essential, high-velocity suction apparatus is already on the market in the United States [50] A further hazard concerns the oil which is entrained with the air-supply to lubricate the turbine The amount of oil used is small (15–30 drops a minute), but it is disturbing to see that one turbine is advertised as using liquid paraffin the use of vegetable oils might be attended by less risk There have been rumours of turbines disintegrating, but no instances of this have yet been published, and, in any event, the head of the hand-piece would probably be strong enough to contain the fragments

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[44] Walsh J P Symmons H F N Z den J 1949, 43, 106
[45] Ingraham R., Tanner, H M J Amer dent Ass 1943, 27, 311
[46] Walsh J P , Symmons, H F N Z dent J 1949, 45, 28
[47] Peyton, F A J Dent 1958 28 191
[48] Nelsen R J , Pelander C E , Kumpula, J W J Amer dent Ass 1953, 47, 324
[49] McEwen R A N Y J Dent 1955, 21, 475
[50] Kilpatrick H. C High Speed and Ultra-speed in Dentistry, p 261 Philadelphia, 1959
[51] Vale W A Brit dent J 1959, 107 333
[52] Gardner, W J , Licklider, J C R. Cited in New Scientist, 1959, 5, 164

Whatever its disadvantages, the high-speed drill is a notable technical advance It will probably never supplant altogether the conventional electric engine, but when it is used it will make cavity preparation less tiring for the operator and less unpleasant for the patient

Annotations

WHAT TO EXPECT FROM OUR BABIES

It may come as a surprise to many that hitherto there have been no accepted weight standards for infants in the first year of life according to birth-weights Without exact information it has seemed reasonable to suppose that most of the smaller infants at birth would at older ages remain at the lower end of the normal weight-range, but this is disproved by Levin et al in a study, published by the Medical Research Council,[1] of 521 healthy full-term and 223 premature London infants

The figures for full-term infants agree closely with those already defined by workers in this country and the U S A Greater interest attaches to the weight records of the premature infants, for these show the overriding influence of an inborn pattern of body size towards which growth proceeds, regardless of accidents such as gestational age at birth Thus, Levin et al find that the mean rate of weight-gain of premature infants was equal to that of infants of comparable age from conception who had remained in utero until term A similar association between gestational age and mean gain in weight during the early months was found in the smaller babies compared with the larger babies with weights above $5^1/_2$ lb at birth (all of whom are traditionally regarded as full-term), the smaller infants having the greater mean increments of weight in their first year In fact, at the end of this time there was a difference of only 10 oz between the mean weights of male infants with birth-weights of 6–7 lb and of 9–10 lb

A physiological standard of growth based on gestational age was suggested by previous assessments of fœtal gain in the later months in utero [2 3], and this was put to the test on a small scale by Young et al [4] There is now little doubt that the standard weight curves for full-term infants can be applied to premature infants by correcting for their age from conception, gauged by birth-weight For example, using Levin's standard curve, the correcting factor for infants weighing $2^1/_2$ lb at birth is $2^1/_2$ months, so a 5-month-old infant with this birth-weight should be compared with the full-term standards of 5 less $2^1/_2$—i e, $2^1/_2$—months On the same basis healthy infants who have a higher than average birth-weight should be regarded as postmature

The weight gains of the premature infants in the series were high in comparison with published figures,[5] reflecting a successful plan of nutrition Most were artificially fed partly or completely, but all the smaller ones received human milk in the first one or two weeks until feeding habits were well established, and a small group under $4^1/_2$ lb were fed on breast-milk alone until they were 8 weeks of age Between 2 and 8 weeks of age the weekly mean gains in weight of this group were lower than those of comparable infants given cow's milk mixtures at the same stage—a difference that has been previously recorded The lower gains can be attributed to the lower protein content of human milk, which has been calculated as insufficient to allow for the "normal" high rate of growth relative to body size between the 28th and 40th weeks from conception In contrast, the breast-fed and artificially fed full-term infants up to 5 months of age gained weight at equal rates, which is to be expected from the amount of protein in an ordinary supply of human milk at this time But, as Levin et al remark, breast-milk is unlikely to provide a satisfactory protein intake for a wasted full-term infant with a higher intake his weight might catch up more quickly with that appropriate for his size On the other hand, it is important to avoid prescribing the usual cow's milk mixtures, with their high protein and electrolyte content, for some infants in whom growth is slow or arrested, such as those with congenital cardiac or renal abnormalities, or those with acute illnesses due to infection (which includes many infants at one time or another before weaning age), otherwise the stress of a high excretory load may precipitate dehydration crises and electrolyte imbalance [6]—a point that is often overlooked in comparing the merits of artificial and of breast feeding Breast-milk is thus the best food for the infant born at term in health this enables him to grow at an optimal rate, and in disease it enables him to withstand phases of stress with the least possible disturbance of his internal milieu

The initial motive in collecting the clinical records of the infants was to provide a background for serum-protein studies These, too, were of special interest in relation to prematurity Analysis showed that, the lower the birth-weight, the lower the serum protein, albumin, and globulin levels at all ages from birth to 3–5 months Grouping the infants by age from conception, Levin et al showed that the serum-protein level corresponds with the maturity of the infant A single curve for infants of all birth-weights shows the changes with age from 28 to 92 weeks from conception This is a new approach which gives a clearer understanding of the changes with age, and now the significance of other variables may be more accurately assessed Several of these were investigated but were found to be without effect on the serum-protein levels, changes in weight were a more sensitive index of nutritional sufficiency

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[1] *Spec Rep Ser med Res Coun, Lond* 1959, no 296 Weight Gains, Serum Protein Levels, and Health of Breast Fed and Artificially Fed Infants Full Term and Premature By B Levin, Helen M M Mackay, Catherine A Neill V G Oberholzer, and T P Whitehead H M Stationery Office Pp 154 16*s*

[2] Reiche, A *Z Kinderheilk* 1915, 12, 369

[3] Huggett A St G *Brit med Bull* 1946, 4, 196

[4] Young, W F, Poyner-Wall, P, Humphreys, H C, Finch, E, Broadbent, I *Arch Dis Childh* 1950, 25, 31

[5] Dunham, E C Premature Infants New York, 1955

[6] Kerpel Fronius, E *in* Colloquia on Ageing London 1958

The report also contains sections on hæmoglobin levels, on serum-non-protein-nitrogen levels in relation to age and diet, and on γ-globulin levels in relation to age This valuable collection of data will be a useful source of standards for all concerned with the development of infants It will undoubtedly promote a more rational approach to the assessment of setbacks to growth due to either disease or dietary insufficiency

GASTRIC OUTLINE AND MOTILITY

THE normal stomach shows a wide range of outline and motility, but the descriptive terms applied to the outline—cup-and-spill, cascade, steer-horn, sthenic, and so on—and expressions such as hyperperistalsis and gastrospasm applied to its motility do not encourage understanding of why any one patient's stomach is as it is

The radiographic outline of the gastric cavity is a model of the mucosal outline, which changes from moment to moment as a result of movement of the mucosal layer on the innermost muscular coat, grosser changes in outline result from contraction of the muscle coats In the longitudinal part of the stomach contraction of the oblique muscle-fibres which form the innermost muscular layer produces a coarsely notched appearance of the greater curvature This feature is often accentuated in the presence of ulceration, and it terminates abruptly where the oblique fibres are replaced by the circular fibres as the innermost muscle layer, at the transition from the longitudinal to the transverse part of the stomach

In the normal stomach peristalsis begins near the cardia, and wave follows wave at a rate of about nine contractions a minute Though stimulation of vagal cholinergic fibres excites peristalsis, and stimulation of adrenergic sympathetic fibres decreases the rate, the pacemaker is probably spontaneous muscular contraction, since excised strips of muscle from the cardia contract at roughly the same frequency as the normal stomach Strong emotional stimuli of anger and anxiety increase the rate and depth of contraction,[1] and fear can temporarily interrupt peristalsis [2] The longitudinal and transverse portions of the stomach probably have inherently different contractile patterns By sectioning cats' stomachs at the junction of the longitudinal and transverse portions Borchers [3] showed that the frequencies of gastric contractions above and below the line of section were quite independent of each other in the longitudinal part four waves of contraction occurred in the same time that two or three occurred in the transverse portion below the section Borchers also showed that section nearer the pylorus was followed by tonic contraction of the pyloric antrum Gastric emptying is not the only factor influencing peristaltic activity The physical state and the nature of the gastric contents are also important, fluid contents pass out rapidly, and food containing a high proportion of fat is retained longest [4]

Lilja [5] has related the appearances during radiological examination with the structure and behaviour of the healthy and the ulcerated stomach The appearances in peptic ulceration are well recognised. Chronic ulceration in the upper and middle thirds of the stomach is associated with shortening of the lesser curvature and increased indentation of the greater curvature in the longitudinal part of the stomach, an ulcer on the upper third of the posterior wall of the longitudinal part with a cascade type of stomach, a penetrating ulcer at the angulus with impaired emptying and dilatation and poor peristalsis in the transverse portion of the stomach, and ulceration in the roof of the transverse portion with concentric antral contraction Lilja suggests that in ulceration of the longitudinal part of the stomach spasmodic contraction of the inner coat of oblique muscle-fibres is later followed by fibrosis, and that in ulceration at the angulus there is peristaltic conduction blockage He suggests, too, that angulus ulceration may destroy a specialised motor centre situated there

The influence of gastritis on the appearances of the stomach outline is debatable Henning [6] stated that broad and thick folds in the stomach were often seen radiologically in a stomach that was histologically normal, and that even with total atrophy of the mucosal layer the rugæ might appear broad and thick Increased folding and irregularity in the stomach outline may result from increased gastric tone Magnus [7] stated that in chronic gastritis a considerable decrease in the number of mucosal glands might be accompanied by a corresponding increase in the areolar tissue in the mucosa, and that accordingly the mucosa itself might not become as thin as it would otherwise be Magnus regarded the mucosal change in pernicious anæmia as purely atrophic, without any increase in the interstitial tissue This true atrophy is limited to the longitudinal part of the stomach and terminates abruptly, the mucosa in the transverse portion of the stomach is either normal or the seat of non-specific gastritis The atrophic changes in the longitudinal part of the stomach in pernicious anæmia involve all coats of the stomach, and the naked-eye appearance is striking Pitman and Laws [8] suspect pernicious anæmia when they observe radiologically a smooth fundus devoid of normal folding, a smooth and rather uniformly tubular longitudinal gastric segment with poor peristaltic contraction, and fine " crushed tissue-paper " rugæ in the empty longitudinal part of the stomach with normal rugal pattern in the transverse part. These findings are complementary to Magnus' account of the histological appearance In this instance the radiological diagnosis of gastritis seems to have passed beyond the stage of mere fancy

The work of Lilja and others shows that the connection between lesions of the mucosa and the substrate of muscular tissue of the stomach wall is closer and more extensive, even in non-neoplastic conditions, than many of us had thought likely

ALCOHOL AND DRIVING ABILITY

A NEW Medical Research Council memorandum [9] describes experiments designed to investigate the effects of small doses of alcohol on a skill resembling car driving [10] Inquiries were also made into individual differences in response to alcohol, particularly in relation to personality ratings, and various methods of estimating blood-alcohol were compared

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[3] Borchers, E *Beitr klin Chir* 1921, 122, 547

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[7] Magnus H A. *in* Modern Trends in Gastro-enterology (edited by F Avery Jones) London, 1952

[8] Pitman, R G , Laws, J W Annual Radiological Congress, British Institute of Radiology, 1959

[9] Drew, G C , Colquhoun W P , Long H A Effect of Small Doses of Alcohol on a Skill Resembling Driving Medical Research Council memorandum no 38 H M Stationery Office Pp 108 *7s 6d* See also *Brit med J* 1958, ii, 993

[10] See *Lancet*, 1959, ii, 51

The subjects of the experiments were 35 male and 5 female members of the staff of the Road Research Laboratory, 1 was aged 58, and the others were between 23 and 40 All were of good intelligence, and most were occasional or moderate drinkers All held driving licences, but they had had varied driving experience The skill tested was that of " driving " a fixed car-like apparatus (a Miles motor-driving trainer) along what appeared to the subject to be a winding tree-fringed road During a 30-minute practice run, blood samples were drawn to familiarise the subject with this procedure, and personality testing was performed the same day A week later each subject began a series of 5 regular weekly 2-hour " driving tests ", after taking one of five standard drinks four consisted of a 20% solution of ethyl alcohol with an alcohol content corresponding to 0 20, 0 35, 0 50, and 0 65 g per kg body-weight per subject, and the fifth was an alcohol-free " placebo " All were heavily flavoured with peppermint and ginger so that it was impossible to detect whether alcohol was present or in what amount During the test run an automatic record was made of " speeds ", tracking errors (i e , variations from a steady course), kerb bumpings, steering-wheel and accelerator movements, brake applications, and gear changes Save for kerb bumps, which were signalled by a loud buzzer, the driver was not informed of his performance during the tests Each test was interrupted every half-hour when samples of blood (by pinprick), urine, and occasionally breath were taken for alcohol estimations

The largest dose of alcohol was equivalent to about 3 pints of beer or 5 fluid ounces of whisky, for a man of average weight, and after each alcoholic drink the blood-alcohol rose sharply to a peak in 30–60 minutes Urinary alcohol rose more slowly and to a higher peak than in blood Tests on breath samples showed that, with the 'Drunkometer' and 'Breathalyser' calibrated to give the corresponding blood-alcohol values, there was good agreement with directly measured blood-alcohol figures similar tests with the 'Alcometer' were satisfactory at first but then became unreliable, possibly because moisture accumulated in the apparatus

The results showed a definite decline in skill with increasing blood-alcohol, a deterioration of about 12% in driving accuracy was associated with a blood-alcohol of about 80 mg per 100 ml Drivers influenced by alcohol tended to steer less consistently and to deviate more and more from the nearside kerb swerves away from the nearside kerb were less quickly corrected, but any tendency to steer into this kerb was more rapidly controlled These responses resemble those of fatigued persons, and they may represent increasing tolerance to error—an increase in the " indifference range "—which may explain the subjective impression of improved precision when in fact skill is diminishing After alcohol, extroverts drove on with maintained speed and many errors, introverts, apparently anxious to demonstrate their efficiency and trying to overcome the effects of alcohol, either slowed down appreciably without necessarily improving performance, or else speeded up, usually with little increase in errors

The time lapse after drinking did not materially affect performance, the effect of alcohol, once apparent, persisted during the 2 hours of the test, possibly because the blood-alcohol did not fall appreciably in that time Age, sex, drinking habits, and driving experience showed no relation to individual differences in response to alcohol In the group as a whole, performance was affected by the lowest dose of alcohol—corresponding to a blood-alcohol of only 20–30 mg per 100 ml —and it seems clear from this carefully designed and conducted experiment that blood-alcohol in the smallest quantities detectable by existing instruments may cause measurable deterioration in skill

INVOLUTIONAL MELANCHOLIA

It has long been agreed that manic-depressive psychosis may start late in life, but whether there is another condition—" involutional melancholia "—is disputed The symptoms are said to differ from those of other depressive illnesses Anxiety, manifested by severe restlessness and agitation, is held to be conspicuous, retardation is usually not prominent, and there is often a rich development of delusions (frequently bizarre and hypochondriacal) centred on feelings of guilt [1] The onset is usually insidious and the previous personality somewhat obsessional Cases of this kind are certainly to be found, but often the picture does not accord closely with this description Perhaps, as Lewis [2] suggested, the rather different manifestations of depression in later life can be explained by the influence of age itself

The evidence for separating involutional from manic-depressive cases is largely genetic Thus Kallman [3] found that the risk of schizophrenia in first-degree relatives of involutional melancholics was 6%—significantly greater than in the general population—whereas the incidence in the relatives of manic-depressives was no greater than the average But Kallman's concept of schizophrenia is wider than that usually accepted here, and doubt has been cast on his findings Kay,[4] for example, in his Stockholm study found an incidence of 2 5–4 2%, but of his 10 probands with schizophrenic relatives the majority had atypical psychoses, and in 3 there had been doubts about classification Also, of the 11 schizophrenic relatives the diagnosis was regarded as doubtful in 4 He concluded that " the risk for schizophrenia among the relatives is not definitely increased " Stenstedt,[5] in a particularly careful study, detected no increase of schizophrenia among the relatives of 307 involutional melancholics Affective illness, however, appeared in about 6% of the first-degree relatives, compared with some 3% in the general population and 12% among similar relatives of patients with manic-depressive psychosis [6] In his cases, as in those of Kay, there were more with prominent exogenous factors than is usual in a group of younger depressed patients Exogenous factors were particularly prominent in the oldest age-groups, where the incidence of affective illness in relatives was also less Excluding cases with presumed exogenous factors, the incidence in relatives was 9 4%—not dissimilar to the figure in cases of manic-depressive psychosis It seems that the earlier the onset the more " endogenous " the illness and the greater the genetic predisposition

Perhaps " involutional melancholia " embraces a heterogeneous group of disorders, including manic-depression of late onset and simple depression with predominant exogenous factors There seems to be little justification for retaining it as a separate diagnostic entity

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Points of View

HÆMATOLOGY IN BRITISH HOSPITALS

PRESENT CONDITIONS AND FUTURE POSSIBILITIES

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HÆMATOLOGY is a relatively new specialty, and in this country hæmatologists were a rare species before the late war. Till then, in England at least, the investigation of blood diseases was carried out in most hospitals in a corner of the general pathological laboratory by the hospital clinical pathologist or his assistant. It seems hardly credible that in 1936 when I was resident pathologist in a London teaching hospital my duties, which were not confined to hæmatology, included carrying out unaided all the blood-counts made on inpatients and outpatients, including collecting the blood, and giving blood-transfusions, as well as collecting blood from the donors and cross-matching it. None of the small staff of technicians helped with the blood-counts.

In the past twenty years or so knowledge of the blood diseases has advanced in many directions and many new and complicated techniques have been introduced; even the vocabulary of hæmatology has been transformed. Vitamin B_{12}, folic acid, Christmas disease, hæmoglobin-S, the Rh blood-groups, Coombs' test, and 6-mercaptopurine were all unknown in the late 'thirties. Each of these familiar terms is now surrounded by a vast literature, and the megaloblastic anæmias, the hæmorrhagic disorders, the abnormal hæmoglobins, blood-group serology, and the chemotherapy of leukæmia have all become subspecialties of hæmatology, each large enough for lifelong study. These remarkable developments pose problems of organisation and administration which I feel have not received the attention they deserve. The particular problem with which I am concerned is how best a hæmatologist and the hæmatological department (if there is one) can be fitted into the organisation of hospital medicine.

PRESENT PATTERN

Today a hæmatologist is almost always a pathologist who has spent nearly all his professional life in a laboratory. He may spend all his time on the investigation of patients with blood diseases, or he may do this in addition to undertaking another branch of clinical pathology—e.g., bacteriology or chemical pathology. More and more, however, I believe the trend in the larger laboratories is towards appointing a pathologist primarily to do hæmatology and to help with other branches only in emergencies or when another member of the staff of the pathological department is on holiday. He probably also supervises the transfusion services of the hospital. In large institutions, and particularly in the teaching hospitals, the laboratory hæmatologist, as I shall call him, often has his own staff of medically qualified assistants.

This pattern is, I believe, almost universal in England—even in teaching hospitals where the medical unit also specialises in hæmatological work and has its own laboratory and staff and carries out hæmatological investigations on the unit's patients. Even then the hæmatological work of the rest of the hospital is usually done by a hæmatologist in the hospital's clinical-pathology laboratory. In Scotland, though there are professorial medical units whose chief concern is hæmatology, hæmatological investigations have in the past usually been carried out in clinical side-rooms by the staff of the physicians in charge of wards, with occasional consultation with or reference to a colleague. This traditional procedure can hardly be expected to keep abreast with the demands of present-day hæmatological techniques, and in some hospitals at least other arrangements are being made.

DAY-TO-DAY DUTIES

The scope of a laboratory hæmatologist's work varies with local circumstances, but, leaving aside the possibilities of teaching and research, his work falls into two main categories.

First, he has to organise and supervise for his hospital a routine or screening service from which the medical staff of all departments can obtain elementary but expertly interpreted hæmatological data on their patients—e.g., hæmoglobin, leucocyte-counts, prothrombin-times, reports on blood-films, blood-grouping and cross-matching tests, and tests for antibodies in antenatal patients. All this work, more often than not, gives normal results and is usually left to the technical staff. It is time-consuming, exacting, and wearisome, but necessary, and it should be supervised by a hæmatologist. Its centralisation in a single laboratory enables this to be done and makes possible the early diagnosis of blood diseases. Shortage of staff often makes it difficult for the hæmatologist to give as good a service as he would like to, and here clinicians can help tremendously by leaving the decision as to what should be done and what need not be done in a particular case to the hæmatologist's judgment.

The second, and more exciting, side of a laboratory hæmatologist's work is the detailed investigation of patients whose blood is abnormal. In this he can often be of real help to his clinical colleagues, for it is almost impossible to diagnose a blood disease exactly without the aid of laboratory tests and experience in interpreting the findings. The central position of his laboratory (this unfortunately is often not geographically true), with all the patients in the hospital potentially a source of hæmatological problems, gives the laboratory hæmatologist remarkable opportunities for the study of a wide range of blood diseases at all stages in their evolution. In this way he rapidly becomes experienced in the investigation of obscure conditions and in advising on the treatment of blood diseases generally; particularly is this true of the management of patients with megaloblastic anæmia, leukæmia, hæmophilia, and hæmolytic anæmia. Recognition of this has led to the hæmatologist sharing more and more in the patient's care, and to the physician in charge often passing over to him the virtual management of the patient's hæmatological treatment and follow-up. This arrangement is a happy one for the laboratory hæmatologist and the physician as well as for the patient.

Finally, the hospital clinical-pathology laboratory may provide a general-practitioner diagnostic service. If so, an important part of this work is hæmatological. I do not deny that this is necessary, but in my view a proper provision of space and staff should be allotted for this work.

RESEARCH

It is every doctor's clear duty to contribute to knowledge of the branch of medicine in which he is working, and facilities for this and encouragement should, ideally, always be available. This is of course easier in the teaching hospitals than elsewhere, and it is unrealistic to suppose that a hæmatologist working in the clinical-pathology laboratory of a busy non-teaching hospital is likely to have time for research In most instances he has barely time to do the basic essentials of his work As for reading, trying fancy techniques, or experimentation, these are impossible But for the fortunate few who have the time, or make the time, the relation between clinician and hæmatologist is important, for the type of research possible to a hæmatologist almost always involves multiple tests on patients, careful follow-up studies, or assessment of responses to treatment It seems right to me that the man who supervises the routine hæmatological work should have the opportunity of carrying out research in the same field, alone or in collaboration with his clinical colleagues I regard it as an unhappy state of affairs if the laboratory hæmatologist is prevented from carrying out research because he has not easy access to patients

It is unfair to the hæmatologist if research on blood diseases is carried out by the clinical staff (who use the hæmatologist's basic data) because they have the time and the necessary apparatus as well as complete access to the patients, while the hæmatologist (who may know more about the problem) is left with his insufficient staff to cope with the routine demands of the whole hospital Under these circumstances a post in the hospital clinical-pathology laboratory is hardly likely to attract first-class applicants

SUGGESTIONS FOR THE FUTURE

I have tried to sketch briefly some of the problems surrounding the hæmatologist and his laboratory How about the patient? He clearly needs to be looked after by a physician who can view him as a whole as well as having his blood disease accurately diagnosed The effects of a blood disease are seldom confined to the blood, almost every system in the body, from the brain to the heart, gastrointestinal tract, kidneys, and skin may be involved For this reason, I have never subscribed to the idea that the laboratory hæmatologist should aim at having beds of his own and complete charge of patients But how can the laboratory hæmatologist's knowledge and experience and his natural desire for some control over the investigations and treatment of patients be reconciled with the undoubted right of clinicians to have full charge of and responsibility for patients in their care? This is the crux of the problem, and I believe it exercises to a greater or lesser degree the mind of every laboratory hæmatologist

My solution (which some may consider a pipe-dream, wild and impracticable) is in essence that hæmatology should be recognised as a subject worthy of a department to itself, and that the department, while retaining its administrative links with the department of pathology or the clinical-pathology laboratory, should have a definite link with the medical side of the hospital The staff of my ideal department of hæmatology would be

1 The laboratory hæmatologist (director of hæmatological laboratory) He should be primarily a clinical pathologist, who has had a good basic training in general pathology, but who has spent most of his professional life working at hæmatology He should not be a clinician, though the more he knows of clinical medicine the better

2 According to the size of the hospital, whether it is a teaching hospital or not, and the character of the teaching, the director should have one or more colleagues of consultant grade One of these should be a consultant physician holding a joint appointment in the departments of medicine and hæmatology He should have beds over which he has full charge, and these beds should be reserved for hæmatological problems He might perhaps have a few general medical beds also The hæmatological physician (as I shall call him), with the laboratory hæmatologist and other members of the department of hæmatology, would act as consultants, if asked, for hæmatological patients throughout the rest of the hospital Such an appointment would provide openings for young physicians with a deep interest in hæmatology but who wish to remain physicians and to have contact with and responsibility for patients with blood diseases At present opportunities for such physicians are almost non-existent in this country Their training should have been as physicians, and they need not necessarily have had any previous experience of general pathology in order to get appointed, though they would find this an advantage They might well develop research interests in such subjects as chemotherapy applied to blood diseases

3 Again according to the size of the organisation, there should be one or more registrars, at least one of whom should be a trainee physician working partly in the laboratory and partly in the wards

4 It would be desirable to have one of the hospital radiotherapists specialise in the application of radiotherapy and radioactive isotopes to hæmatological diseases He might well have some status in the department of hæmatology

5 An adequate staff of technicians, secretaries, laboratory clerks, &c I believe that most laboratories are understaffed.

The size of the hæmatology department will naturally vary greatly from hospital to hospital Nevertheless, the principle of a close link between hæmatology and medicine could, I think, be applied almost anywhere The duties of the department would broadly be (the order is not meant to have significance)

The provision of a routine, or screening, diagnostic hæmatological service for the whole hospital

The investigation and exact diagnosis of cases of blood diseases throughout the hospital, the supervision of treatment of inpatients with blood diseases in the department's beds, and the provision of an advisory service for the rest of the hospital

Organisation of follow-up clinics for blood diseases, including megaloblastic anæmia, hæmophilia, leukæmia, and polycythæmia clinics, as well as joint clinics, with the appropriate clinical staff, for blood abnormalities which are commonly associated with another disease—e g, anæmia and disease of the gastrointestinal tract

The provision of a blood-transfusion service for the hospital, excluding giving blood and bleeding donors

The conduct of research and teaching

" The good husband is now the domesticated husband—the man who, when he has finished his work at the factory or the office, spends his evenings and his weekends not with his workmates but at home with his family, enjoying common fireside relaxations with them, or else 'pottering' round the house maintaining or improving its comfort and appearance Once he sought to escape from the crowded shabbiness of his home to the warmth and conviviality of 'pubs' or the club rooms of voluntary associations, and inevitably in the process he developed social interests and wider loyalties But now the new man stays at home, and he is likely to find burdensome and repugnant any activities or interests that force him to leave the family circle and to forgo part of his domestic privacy and comfort If his outside contacts are weakened and reduced in favour of his home ties, this will affect all his group relations Reduced attendance at trades-union meetings, at Friendly Societies and other club activities, at political discussions, and at all forms of outdoor mass entertainment and activity will inevitably affect his attitudes towards the social institutions they serve Thanks to television and radio he is, as a spectator and listener, able to sit at home and participate in these activities to a much greater extent than ever before But the participation is that of a detached, isolated observer served by technicians who are able to multiply his eyes and his ears, and by commentators able to develop his professional critical abilities "—MARK ABRAMS, *Listener*, Nov 26, 1959, p 915

Special Articles

THE COST OF DRUG TREATMENT

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Man's addiction to pills and potions is as old as history, but until recently reliable evidence has been lacking about such changes as may have occurred over the years in the relative proportion of our national resources which has been devoted to the provision of drugs

Official anxiety about such expenditure dates from the time when this first became a charge on public funds, and has become more vocal with the much-publicised rise in the national drug bill from £31 million to £62 million which took place between 1949 and 1958 For the first time this change in the method of payment for medicines has permitted an assessment of their national consumption in terms of money, and has activated the concern which is always evident in matters of public accountability the equanimity with which a comparable dissipation of national resources was regarded while the transactions remained in private hands is a familiar phenomenon

The discovery by politicians that a comprehensive health service—even though it is no longer literally " free and open to all "—is an even more expensive business than they had anticipated has provoked a crescendo of Ministerial inquiries and exhortations which conveys a general implication that either the rapacity of patients or the complaisant negligence of doctors, or both, must be held responsible for a considerable proportion of the rising costs The administrators' failure to evolve a less expensive system of supplying the drug to the patient, and the politician's responsibility for inflation, are less frequently inculpated in public discussion, although in fact allowance for the falling value of the pound during the decade in question reduces the " real " increase in the drug bill from 100% to 40%

Official homilies are couched in general terms, and often deal with figures so astronomical as to be meaningless to the average doctor The present paper is based on a clinical lecture to medical students, directing their attention to the average weekly cost of some widely used forms of medical treatment with drugs as they are dispensed in general practice This seemed a simple enough undertaking, but we soon discovered that the problem was both more complex and more intriguing than would appear at first sight Finding that our ignorance of the subject was shared by many of our colleagues we considered the facts worthy of wider circulation

Method of Costing Prescriptions

The total cost of a general practitioner's prescription is the sum of four separate items (1) the basic cost of the drug, (2) the " on-cost ", which is 25% of the basic cost, and represents the permitted margin of gross profit to the pharmacist, (3) a container allowance of about 1½*d* , and (4) a dispensing fee of at least 1*s* 2*d* for the pharmacist's professional services Under present conditions the patient contributes 1*s* to the cost of each prescription It will be seen that the " basic cost of the drug to the N H S " may be a very different matter from the actual charge on the Exchequer

Indeed, the system has some curious results The " basic cost " of half a grain of phenobarbitone three times a day for a week is 1*d* The " on-cost " raises this to 1¼*d* and the container allowance to 2¾*d* A dispensing charge of 1*s* 2*d* recompenses the pharmacist for the professional skill involved in dispensing the prescription The total cost of the pennyworth of phenobarbitone is therefore raised by more than 1600% to 1*s* 4¾*d* The example of terramycin shows the working of the system in a different way The basic cost of one gramme of this drug daily for seven days is £1 19*s* 8*d* On this the pharmacist is allowed a profit of 9*s* 11*d* and a dispensing fee of 1*s* 2*d*, raising the total cost of a week's supply of the drug to £2 10*s* 10½*d*

Examples

The weekly cost of treatment with some familiar drugs in average doses as prescribed by the general practitioner is set out below to the nearest penny The figures relate to prices prevailing in July, 1959, and have been averaged to allow for occasional variable factors The " prescription charge " of 1*s* is excluded from consideration here, but it is universally applicable, and has the effect of reducing the cost to the Exchequer by 1*s* in every instance

CARDIOVASCULAR DISEASE

The treatment of *heart-disease* is generally inexpensive The average weekly cost of digitalisation varies from 1*s* 5*d* (digitalis leaf *N F*) through 1*s* 6*d* (tincture) and 1*s* 9*d* (digoxin) to 2*s* 0*d* (digitoxin) The weekly injection of mersalyl costs 1*s* 8*d* (basic cost of the drug is 3½*d*) but four days of ' Saluric ' costs 5*s* 8*d* and a week's supply of hydrochlorothiazide 10*s* 6*d*

The long-term medical management of *hypertension* is usually a more expensive business, the average weekly cost of ' Serpasil ' being about 2*s* 9*d* , ' Ansolysen ' 6*s* 3*d* , ' Apresoline ' 6*s* 7*d* , ' Tenormal ' 7*s* 10*d* , and ' Inversine ' 8*s* 3*d* If pilocarpine is administered simultaneously to control side-effects the cost is raised by another 5*s* 6*d* weekly

The treatment of *angina* costs 1*s* 5*d* per week with nitroglycerin, 1*s* 11*d* with ' Peritrate ', 2*s* 5*d* with ' Mycardol ', and 6*s* 2*d* with ' Marsilid '

With regard to *anticoagulant* treatment, heparin is notoriously expensive (£2 17*s* 6*d* for 48 hours), dicoumarol at 3*s* 2*d* and ' Dindevan ' at 3*s* 0*d* weekly much less so

NEUROLOGICAL DISORDERS

The cost of treating *epilepsy* varies from 1*s* 5*d* weekly (phenobarbitone) through 2*s* 6*d* (' Epanutin '), 4*s* 3*d* (' Mysoline '), and 5*s* 6*d* (' Tridione ') to £1 6*s* 6*d* (' Nydrane ')

For the prophylaxis of *migraine*, Gowers' mixture costs 2*s* 5*d* weekly, ' Stemetil ' 6*s* 6*d* However, the treatment of an individual attack with three tablets of ' Cafergot ' may cost from 1*s* 6*d* to 2*s* 6*d* , and with ' Migril ' from 2*s* 1*d* to 3*s* 11*d* , depending on the number of tablets prescribed at a time

Myasthenia gravis is a fairly expensive illness In low average dosage of two fifteen-milligramme tablets three times daily ' Prostigmin ' costs 6*s* 6*d* weekly, comparable dosage with ' Mestinon ' 15*s* 3*d* For parkinsonism ' Artane ' (3*s* 1*d*) now costs no more than tincture of stramonium or hyoscine hydrobromide ' Cogentin ' (6*s* 2*d*) is twice as dear, but ' Kemadrin ' (2*s* 8*d*) represents one instance where the prescription of a proprietary drug represents an economy

Wilson's disease costs 3*s* 4*d* weekly treated with calcium versenate, 4*s* 11*d* with dimercaprol (BAL), and about £15 10*s* 0*d* with penicillamine

INFECTIONS

Sulphonamides are cheap, a week's supply of sulphamezathine costing only 3*s* 2*d* The weekly cost of a daily injection of one mega-unit of penicillin is 10*s* , but oral penicillin V in tablet form in dosage which most would consider no more than adequate for the treatment of a severe infection (one gramme daily) might cost £1 7*s* 6*d* weekly, or £2 19*s* 7*d* in suspension In the latter form, indeed, oral penicillin is probably the most expensive antibiotic in general use, the average weekly cost of the others varying from £1 13*s* 4*d* ('Chloromycetin'), to £2 5*s* 0*d* (erythromycin), £2 7*s* 1*d* (aureomycin and 'Achromycin'), £2 10*s* 10*d* (terramycin), and £2 18*s* 2*d* (neomycin)

Streptomycin costs 14*s* 5*d* weekly and isoniazid only 1*s* 10*d*, but *p*-aminosalicylic acid (P A S) £1 2*s* 11*d*

ENDOCRINE PREPARATIONS

The cost of treatment of *diabetes mellitus* is almost independent of the type of insulin employed Twenty units of soluble insulin twice daily costs 5*s* 1*d* weekly, protamine zinc insulin or globin insulin in comparable dosage 5*s* 3*d* A syringe and one packet of needles costs 8*s* 1*d* Tolbutamide (5*s* 10*d*) is comparable in cost with insulin

In the treatment of *hypothyroidism*, L-thyroxine (1*s* 10*d*) is only slightly dearer than thyroid extract (1*s* 6*d*) In Graves' disease a week of methylthiouracil costs 1*s* 5*d*, a week of 'Neo-mercazole' 4*s* 0*d* In the treatment of *Addison's disease* ten grammes of sodium chloride daily costs 2*s* 7*d* weekly, fluorohydrocortisone 6*s* 6*d*

The comparative costs of various therapeutic routines in *rheumatoid arthritis* are of some interest Aspirin costs 1*s* 10*d* weekly, calcium aspirin 2*s* 7*d*, 'Paynocil' 6*s* 0*d*, 'Butazolidin' 8*s* 7*d*, prednisone 15*s* 5*d*, and cortisone £1 0*s* 10*d*

EMOTIONAL SYMPTOMS

Modern preparations for *sleeplessness* are not expensive Nightly 'Soneryl' costs 1*s* 11*d* weekly, 'Seconal' 2*s* 1*d*, 'Tuinal' 2*s* 8*d*, and 'Carbrital' 3*s* 2*d*

'Amytal' (2*s* 0*d*) remains the cheapest ataractic, 'Largactil' costing 3*s* 10*d*, 'Oblivon' 4*s* 0*d*, and 'Equanil' 4*s* 4*d*

'Dexedrine' in tablets costs 1*s* 5*d*, in 'Spansule' form 2*s* 6*d* The new antidepressive preparation 'Tofranil' costs 17*s* 6*d* weekly for average maintenance dosage

Discussion

These figures demonstrate the low basic cost of many of the drugs most widely used It is a remarkable tribute to the efficiency of the pharmaceutical industry that a week's supply of phenobarbitone or digitalis in reliably standardised dosage can be furnished by the industry for a "basic cost" of 1*d*, with dextroamphetamine for 1½*d*, and with thyroid extract for 2*d* In such instances a distributive cost which may exceed 1500% is startling, while the "on-cost" in the case of the more expensive preparation (e g, 11*s* 4½*d* on seven grammes of neomycin) also makes an appreciable contribution to the final cost of the prescription In general the cost of distribution adds 50% to the basic cost of the drugs considered above —a figure which suggests that distributive costs may account for one-third of the total national drug bill

The dispensing fee is intended as remuneration for the pharmacist's professional services in making up the prescription In the calculations noted above the flat-rate dispensing fee of 1*s* 2*d* has been added to the basic cost of the drug, but in fact this is the minimum The dispensing fee on 42 tablets of phenobarbitone is 1*s* 2*d*, but on a prescription for 350 tablets it is 4*s* 0*d* The compounding of medicines in the pharmacy is steadily declining, and at the present time probably rather more than three-quarters of all National Health Service prescriptions are for tablets the dispensing of which does not call for any high degree of professional skill

Expensive Drugs

Expensive drugs are of three kinds first, those which are genuinely expensive to manufacture (e g, penicillamine), secondly, new drugs in which the costs of development must be recouped by an initially high price (e g, nydrane), and, thirdly, special preparations of banal remedies (e g, phenobarbitone in spansule form)

Penicillamine is produced by a complex and expensive chemical process, and it has no use whatever except in the treatment of Wilson's disease The high cost of the drug covers no more than the expense of manufacture Its use represents a real advance in the treatment of this distressing disease It goes far to correct the biochemical anomaly which is at the root of the condition, and may produce considerable symptomatic improvement It is not a cure and it rarely restores social efficiency On the other hand its employment may allow home rather than institutional care It is difficult to see any justification for denying its continued administration to any patient with this disease who obtains unequivocal benefit from it, but at an average annual cost of £750 its prescription cannot but cause the physician some concern

One special reason for this is that although the day-to-day care of the patient may have passed into the hands of her general practitioner the drug is always distributed from a hospital pharmacy, and the maintenance of two sibs with Wilson's disease may saddle the hospital with an annual expenditure of £1500 or more The physician knows that no special financial allotment is made in such cases, and that the money must come from an annual Ministerial allowance for running expenses which is regularly thousands of pounds below what the hospital administration has carefully estimated as necessary to provide an efficient service In fact he knows that the provision of such treatment may reduce the amount of cash available to the hospital for the purchase of such requisites as surgical instruments

The instance of penicillamine emphasises another anomaly of wider implications It is cheaper to supply drugs from a hospital dispensary than by means of a general practitioner's prescription dispensed by a private pharmacist The hospital has the advantage of bulk purchase, there is no "on-cost", and the proportion of the hospital pharmacist's salary which can be related to the service involved in a single prescription is very much less than even the minimum dispensing fee of 1*s* 2*d*[1] However, the system of hospital budgeting is such that some hospital administrations have found it necessary to advise their medical staffs to cut down the treatment of outpatients with drugs from the hospital dispensary in favour of the patient's earlier reference back to his general practitioner, even though there are many instances where hospital supervision is a convenient as well as an efficient and economic temporary arrangement Paradoxically, the hospital, in an attempt to balance its own budget, finds itself obliged to advise a course of action which involves an increased charge on public funds

Difficulties also arise in relation to the second group of expensive drugs At a time of unparalleled advance in pharmacology the doctor is subjected to a daily barrage of advertisements for new preparations, many of which are expensive A few of these find an established place in current therapeutics For example, artane, introduced as a rather expensive proprietary preparation ten years ago, is now probably the most widely used drug in the treatment of Parkinson's disease and has become slightly cheaper (as well as more convenient and more chemically stable) than the traditional hyoscine and stramonium mixtures it has largely displaced However, had artane not proved its worth during the course of sporadic and haphazard employment over the course of a few years by thousands of doctors—at a time when it was still an expensive and untried drug—the benefit of this advance might never have been extended to the majority of patients with parkinsonism. This process of assessment could have been expedited by the early commission and publication of controlled therapeutic trials. Modest expenditure on this branch of clinical research would be an economic investment: for example, a small-scale investigation in this department[2] defined the limited role of one of the more expensive modern anticonvulsants in the management of epilepsy, and has probably rendered its widespread routine employment a little less likely.

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[1] Martin, J P Social Aspects of Prescribing London, 1957

The third type of expensive drug—the special preparation or combination of banal remedies—is an Aunt Sally for the critic, and indeed the marketing of expensive hæmatinic *olla podridas* and unholy combinations of vitamins and sedatives by otherwise reputable firms greatly strengthens the hands of those who would like to restrict the doctor's freedom to prescribe. But in fact many of the preparations in this group are extremely valuable. The long-acting effect of a spansule of phenobarbitone may make all the difference in the control of the difficult epileptic whose fits occur in the early morning. And although hard words have been used by purists about multi-vitamin preparations it would be negligent as well as doctrinaire to withhold them in the complex and ill understood metabolic disturbances manifested by a malnourished alcoholic or a patient with an obscure malabsorption syndrome.

It is clear also that the cost of drugs cannot be considered in isolation from other aspects of medical care. The prescription of oral penicillin in massive dosage in place of the less expensive injection not only may be imperative in the needle-shy child but also may be economic in a distant farm-labourer with a respiratory infection, to whom each visit may involve opening half a dozen moorland gates. Six months of tofranil for a depressed patient may push up the national drug bill by £30. The fact that such expenditure has saved £300 by averting admission to hospital will be sought in vain among Ministerial statistics.

That some doctors indulge in what some other doctors regard as over-prescribing cannot be doubted. But attention is less frequently drawn to *under-prescribing* by doctors who for one reason or another—sometimes undoubtedly for fear of administrative criticism from above—fail to give their patients the benefit of expensive remedies scientifically validated as outstandingly effective. In the same way it is often inferred that the higher average cost per prescription encountered in more prosperous localities[1] is due to extravagant or "excessive" prescribing. Since this high average prescription cost also correlates with a lower than average morbidity, a decreased frequency of prescription per patient, and a smaller than average number of patients per general practitioner, it could be quoted with at least equal justification as demonstrating a high and effective standard of medical practice worthy of more widespread emulation. Attractive though the economical doctor may be to the administrator, evidence is lacking of any correlation of low-cost prescribing with professional efficiency, and it seems improbable that even a Treasury officer would regard such parsimony as a quality to be sought in the choice of his own medical attendant.

In fact, although the view that extravagant prescribing makes a material contribution to the national drug bill is evident in much that is said and written on the subject, any factual basis for such a suspicion is lacking. It is certainly implicit in two measures which have been repeatedly recommended in the hope of holding back rising expenditure—limitation of the quantity of drugs to be permitted on a single prescription, and the employment of cheaper remedies where this is possible. The first of these is unexceptionable so long as it is not applied in the case of the very large number of chronic patients, in every branch of medicine, who require permanent or long-term maintenance dosage with relatively infrequent professional attendance. Any limitation of the quantity of drugs available on a single prescription in these cases would materially *increase* the cost of treatment, besides wasting the time of the doctor and the dispenser. Indeed the contribution of any restriction of quantity could hardly be more than to discourage such waste as now occurs in the treatment of acute illnesses.

The frequently reiterated Ministerial exhortation to employ cheaper remedies wherever possible presents greater difficulties, and is indeed not easy to reconcile with a deeply ingrained professional attitude of doing the best possible for each individual patient. It is easy for a Civil Servant to write such a recommendation into a memorandum but a very different matter for the doctor to offer something "second best" to a sick patient. We are indebted to a distinguished academic colleague for a practical suggestion towards the resolution of this ethical difficulty—that a small hospital be established for the carefully controlled assessment of cheaper treatments. He suggested that such a hospital might perhaps be situated conveniently for Whitehall, so that it could at once serve the physical needs and satisfy the public spirit of senior Civil Servants and politicians.

Conclusions

The desire to find a scapegoat to be held responsible for any unpalatable occurrence is universal, and is evident in the tendency to saddle the doctor, the patient, or the pharmaceutical industry with responsibility for the rising national drug bill. It is our contention that this is in fact the inevitable price of the present scientific revolution in medicine. The benefits of this revolution are evident in almost every field of vital statistics, as well as in an inscrutable but enormous reduction in the total amount of suffering in the community. But they cannot be obtained unless they are paid for. The tempo of medical research shows no signs of slackening, but rather the reverse. It is worth noting that the pharmaceutical industry alone spends a sum of money on research each year which is appreciably greater than the total annual budget of the Medical Research Council: even in the matter of basic pharmacological research its output dwarfs anything that can be achieved with the inadequate facilities afforded in the exiguous pharmacological departments of the universities. Unless the pace of research slackens—in which case neither the medical profession nor the industry will deserve well of the public—the drug bill, like the cost of the Health Service as a whole, is bound to rise. Whether such an increase need outstrip increasing national productivity is not a problem for the doctor. In the meanwhile an annual increase of 3·4%, at a time of previously unparalleled progress in therapeutics, seems to us to have caused quite disproportionate surprise and alarm.

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[2] Wilson, J., Walton, J. N., Newell, D. J. *Brit. med. J.* 1959, i, 1275.

PRIORITIES IN SOCIAL WELFARE

ADDRESSING the National Council of Social Service on Dec 8, Prof FRANÇOIS LAFITTE suggested that since 1948 we had been trying to extract a quart of welfare and defence from a pint of resources. As a result our actual social programme differed from the proposals of the famous blueprints for post-war social reconstruction.

The blueprints had presupposed a massive investment in re-equipping the social services with buildings and institutions good enough and diverse enough to serve the widened aims of social policy—health centres, small welfare hostels, secondary modern schools, hospitals, dental clinics. In fact 1954 was the first post-war year in which the physical volume of capital resources put into the social services (including education) even reached the inadequate level of 1938. Until we had got over the hump of rearmament and the housing boom, in real terms the claims of the health service were "frozen" and education was confined to its "essential fabric". However, by 1958 the health service was allowed to take 10% more real resources than in 1951 (all the increase occurring since 1954), but top priority was given to education (which received an increase of 36%).

Turning to the future, Professor Lafitte foresaw that the margin of public funds for welfare in the nation's budget would rise from initially £70 million a year to at least £400 million a year by 1964. This could either be returned to consumers, through tax reliefs, for individual enjoyment, or used to improve the social services for communal enjoyment. A central issue of public policy was how to balance the claims of individual and communal enjoyment. A large part of the "welfare margin" was already earmarked by the Government for improving education. Eventually education was likely to need up to £200 million a year extra. Education remained the Government's no. 1 priority. "It is also mine," Professor Lafitte added, but he thought that after 1965 we could hope for a refurbishing of the health service's assets, to be followed in the early '70s by a housing boom, as the post-war "bulge" of children and their nearly as numerous successors took to marrying and home-making.

Since the war precedence had been given to the social services which help the ordinary family—maternity and baby welfare, family allowances, schooling, libraries, and medical and dental care. Without neglecting these common services ought we not, he asked, to be doing more for the minorities with uncommon needs? If society did not adequately provide for those who needed support to offset handicaps, could it really be proud of how well it cared for the social needs of the normal majority? We should face the fact that economic advance was steadily bringing the mass of wage-earners into the lower middle-class income ranges. It would be well for society if policy did more to quicken the spread of some of the lower middle-class virtues, such as budgeting over longer periods than a week or a month, and setting money aside for emergencies and old age. Most ordinary earners were being carried so far above a subsistence standard of living that it was becoming steadily less reasonable to want a social policy which assumed that no great number of fully employed citizens could house themselves decently unless the State built the dwellings and subsidised the rent, or that hardship was caused if people had to pay any appreciable part of the cost of welfare milk, school meals, spectacles, dentures, and other simple requirements.

In view of the growing prosperity of the ordinary citizen, Professor Lafitte would himself select, after education, the following social priorities:

Services for the mentally ill or handicapped should be humanised and transformed in the direction of community care and aftercare. Policy was already committed to this reorientation, but its implications had scarcely yet been studied. Its attraction was that it would avoid institutionalisation, its danger was that it might mean a transfer of defenceless souls from skilled to less skilled care—or to no care at all. If properly carried out, it would not be cheaper than the old method: it would be more humane and sensible.

Diversification and re-equipment of penal institutions were urgent, because they were nearly all presupposed by the Criminal Justice Act, which it was becoming fashionable to decry before it had been given half a chance to work effectively.

Family welfare services should be remodelled and perhaps fused to form a general all-purposes service.

Services for handicapped minorities were still inadequate and often less effective than they could be, because of their multiplicity.

Extra age benefit for the over-seventies would recognise advanced old age as a special handicap. Most old people of today had lived through two world wars, two post-war inflations, and an era of mass unemployment. Their chances of saving must have been minute, compared with those of the present working population.

Social work and training should be expanded, for the "underdog" services were also undermanned services.

Teenagers and the Bulge presented society with a challenge which we had partly failed to meet. The main improvements in education would come after they had left school. We kept adolescents at school longer than we used to, yet they matured earlier, and we had not really learnt how to handle, and what to teach, teenagers who were neither bookish nor intellectual, and who were no longer children. For the first time in history working lads and girls had the means to assert their independence by dressing, spending, and behaving in distinctive ways. If some of them went off the rails, were they not less to blame than the inflated economy, which gave them the means to snap their fingers at Dad, and the earlier neglect of their education?

MEDICAL JOURNALS FOR DOCTORS IN DEVELOPING COUNTRIES

THE British Supporting Group for the World Medical Association invites doctors in the United Kingdom to participate in a project for the regular supply of used British medical journals for doctors in "underdeveloped" countries—more especially in the Commonwealth—who, for various reasons, have at present little or no access to British medical literature. A pilot experiment for doctors in India is to be started early in the New Year. The scheme is to be essentially personal, an individual donor of used journals being placed in direct postal contact with an individual recipient. The honorary secretary of the British Supporting Group will provide a stamped and addressed envelope or wrapper to the donor, who, once a month, will post his journals to the recipient allotted to him. The journals which it is proposed to invite donors to send are the *British Medical Journal*, the *Practitioner*, and *The Lancet*.

The scheme will, it is hoped, help to disseminate knowledge of British medicine and its methods among doctors in less developed territories. The journals will be of value not only to individual readers or groups of readers, but also in forming a nucleus for a local reference library

Doctors who may be willing to take part are invited to get further information from the honorary secretary of the British Supporting Group for the World Medical Association, B M A House, Tavistock Square, London, W C 1

BIRTH CONTROL IN AMERICAN POLITICS

FROM A CORRESPONDENT IN THE UNITED STATES

CONTRACEPTION has become a major political issue here Last July the Draper Committee, who had been appointed by President Eisenhower to consider foreign military and economic aid, said in their report that the United States should give help, to nations that asked for it, " in the formulation of practical programs to meet the serious challenge " posed by populations growing beyond their means of support, and, answering a question, General Draper said that birth control was in the committee's purview This recommendation, which has not been acted on, attracted little attention until, in November, the Roman Catholic bishops issued a statement opposing " any public assistance, at home or abroad, to promote artificial birth control "

This statement has been criticised by other religious groups The head of the National Council of Churches (a Protestant organisation which, like the Roman Catholic Church in America, claims 39 million adherents) said that the decision of a President should be for his individual conscience and not be determined by the Roman Catholic Church—though he thought that private agencies would be a more suitable source of birth-control information than the Federal Government. The New York Board of Rabbis said that birth-control aid should be given to countries that requested it But President Eisenhower (a Presbyterian) has said emphatically that birth control is not a proper Governmental responsibility He expressed respect for the Catholic Church, for which, he said, " this thing has   religious meaning ", and though he added " this has nothing to do with Governmental contacts with other Governments ", it is widely held that his disclaimer is partly at least in deference to Roman Catholic views—especially since he made no adverse comment when the Draper Committee's report was first published, and it is said that it was on his insistence that the committee considered birth-control assistance [1]

The Protestant Council of the City of New York (which recently led the successful fight to make birth-control instruction legal in the city's hospitals) has complained that the contrary views of members of Protestant communions should also be taken into account, and a Presbyterian writer said that if the President's deference to the beliefs of certain sects was carried to its logical conclusion he would not let the Government contribute to armaments, because the Quakers are pacifist

The question has assumed political importance, not because of a split along party lines—many prominent Democrats have endorsed the President's attitude—but because at least two of the aspiring candidates for the Presidency next year are Roman Catholics, and the attitude of each to this issue may be taken as an indication of how his religious beliefs might affect his actions in general if he were elected President

There is some irony in the debate about American aid to foreign countries to promote birth control when many American States have laws restricting birth control, for instance, a Connecticut State law prohibits the use of contraceptive devices and forbids doctors to advise their use, even to save the lives of patients This law is being challenged before the Connecticut Supreme Court of Errors, and on Dec 22 the court unanimously upheld the " constitutionality " of two 1879 statutes which forbid the presenting of or use of birth-control drugs or devices [2] The plaintiffs, Dr C Lee Buxton, chairman of the obstetrics department at Yale University, and five unidentified patients of his, have announced that they plan an appeal to the Supreme Court

Personal Papers

AFTER NEARLY THIRTY YEARS

Plato says in *The Republic* that " the most skilful physicians are those who, from their youth upwards, have combined with the knowledge of their art the greatest experience of disease, they had better not be robust in health and should themselves have suffered from all kinds of illnesses " This method of instruction is not included in the medical curriculum and is fortunately imposed on only a few doctors Being one of this group and having had a full dose of Plato's prescription in my mature years, I propose to submit his theory to the test of my own experience

The illness was severe but never clouded my brain On the evening of Feb 17, 1930, after a few hours' premonitory symptoms, I became paralysed from the waist downwards, from transverse myelitis, while I was well on the way to recovery from a brief severe septicæmia The paralysis, which I unexpectedly survived, left a considerable legacy of disability, principally affecting locomotion, bladder, and bowel—a spastic paraparesis Certain aspects of this illness have already been recorded [3-5]

THE PATIENT'S FIRST QUESTION

The illness was considered hopeless, absolutely so I myself was well aware of its gravity. Nevertheless, the next day I asked my physician " What do you think are the chances of my recovery? " He replied without hesitation· " I really do not know If I were pressed for an answer, I should say fifty-fifty " I was in no mood to dispute this kindly verdict, so I thanked him and said it was very encouraging, and we left it at that

On the twelfth day the distinguished brain surgeon, the late Sir Percy Sargent, kindly came to see me Before he left he came to my bedside and said, very, very kindly " I have now got a complete grasp of your case It is very rare I have seen only two similar cases I cannot tell what is going to happen to you, but I can say this, that I do not see any absolute reason why you should not, ultimately, almost completely recover, except for a slight weakness of the peroneal muscles of your right leg " This verdict, to one still completely paralysed, was a wonderful exhibition of clinical skill In my completely darkened sky, Sir Percy placed the bright star of hope That star never set. He had, however, no expectation that I would survive No-one could have been more astonished than he, when we met about a year later at the meeting of the Association of Surgeons in Belfast, he himself *told me* so

These answers throw a little light on the vexed question of what the doctor should tell a patient suffering from hopeless illness He should not tell him anything disagreeable unless the patient really wants to know He should not tell a lie He should recognise the cases in which the truth is a relief from doubt, uncertainty, and fear He should never forget that he may be wrong He should speak very kindly and always if possible leave a ray of hope The second answer was worth the world to me

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[1] *New York Times*, Dec 6, 1959, sect E, p 3

[2] *ibid* Dec 23, 1959, p 1

[3] Disabilities and How to Live with Them p 114 London, 1952 (Published by The Lancet Ltd , 7, Adam Street, W C.2.)

[4] *Lancet* 1955, ii 25

[5] *ibid* 1956, ii, 35, 1256

THE EMOTIONAL REACTIONS

It is the emotions that rule the lives of men In sudden severe illness the emotions are deeply stirred They should not be lightly interfered with The emotional complex of different people differs as much as their faces do, built-up by the daily habits of years A crisis, such as an illness, should not be used to upset them

Very curiously I had no emotional reaction to the actual onset of paralysis The tragedy had happened, and I simply accepted the fact There was no pretence about this, and I was—and I felt—as cheerful as before

The true meaning of this equanimity became apparent on the evening of the ninth day I was alone The fire had died down It was a dull dismal evening in late February Suddenly there swept across my mind a full realisation of what had happened to me, that I, laid in bed, could do nothing but raise my arms and move my head from side to side on the pillow, that I might continue to be utterly helpless as long as I lived, till death should release me All at once I could have shrieked and shrieked in a frenzy of despair What I did was to say to myself that this was not a nice thing to think about, and that I must think of something nice In a few moments the spectre fled, and I was calm again A horrid thought like this must be routed at its first onset

It recurred—only for a moment—the next evening And never again

On the eleventh day, a peculiar choice faced me—the free choice of life or death I said to my surgeon, on his morning visit, that I was on a slippery slope and if no change occurred would die in precisely four days He agreed that this would happen unless I resumed taking nourishment, and suggested Bengers food I was very emaciated Fourteen days earlier, I had been put on a waterbed to prevent bed sores because I was so thin For 11 days I had (by my own desire) lived on nothing but water and oranges (6–8 a day) I was mere skin and bone It was a dreadful choice Without telling her why, I put the question to my wife, the other person deeply interested, whether it was worth my continuing to live, even if paralysed She replied emphatically " Yes " So I asked for Bengers food After all, the other choice would have meant a cowardly exit from life

These emotional reactions are of great interest The delayed emotional upset, in its lateness, its suddenness, and its intensity is not unique, nor characteristic of a doctor The absence of an hysterical outburst is due to the medical training It is explained by Dr John Brown in *Rab and His Friends* The medical students at Edinburgh Infirmary were on their way to the theatre to watch an operation for advanced cancer of the breast This was about 1815, before the days of anæsthesia, and it must have been a dreadful spectacle " Up ran the youths, eager to secure good places, in they crowded full of interest and talk ' What's the case ? ' ' Which side is it ? ' Don't think them heartless they are neither better nor worse than you or I in them pity—as an *emotion*, ending in itself or at best in tears and a long drawn breath, lessens, while pity as a *motive* is quickened and gains power and purpose " This diversion or redirection of the emotions from their ordinary passive manifestations into an active channel is an essential part of the training of a doctor The ordinary manifestations of an emotion cause mental confusion and paralysis of action Its diversion into channels of activity induces presence of mind and stimulates helpful action This trained instinct prevented the hysterical attack

On the twelfth day, I had a further diversion of the emotions From the moment that Sir Percy Sargent implanted in me the hope of recovery, all my emotions and all my spiritual, mental, and physical powers were directed to one purpose—recovery It was my single aim, my distant goal

LEARNING TO WALK AGAIN

I learnt to walk as a child does, instinctively, by trial and error, by repeated effort The beginning was slow and required patience Not till six days after Sir Percy's visit did the first flicker of movement appear in my great toes I have a vivid memory of my happiness, the next day, when I could move both great toes Then in slow succession came movement of all the toes, the ankles, the knees, and in the end the hip-joints My excellent Swedish masseur came for an hour a day, seven days a week, and on the day when I first got out of bed, precisely three months from the onset of paralysis, I was able to walk to and fro in front of the fireplace holding on to the mantelpiece surely a triumph for massage

Three weeks later I left the home for the seaside

> " Like a child sent with a fluttering light
> To feel his way along a gusty night " *

just able with stick in my right hand and my nurse on my left to walk slowly and uncertainly a little way Henceforth, the master word was perseverance, day in, day out, several times a day It would be idle to describe the detail, since Nature adapts with great precision the technique suited to each case, but there is one point I should like to dwell upon

I learnt very soon that I was doomed to fall frequently, and this has gone on all through the years It was not a defect of balance, for I could stand on either leg, but if my balance was upset my legs were so slow in moving that they could not always save me I found out in time all the causes of upset, but it was not always possible to avoid them Later on, I set myself to learn the art of falling safely (and if possible, gracefully) by diligent practice in a big room This was invaluable I also learnt and practised the special technique for rising unaided Let me give an example of the value of such practice

I was coming out of the front door of a Scottish hotel (many years later) On the landing was a wire mat, which curled up as I stepped on it, and caught my foot, precipitating me head foremost down five steps on to the hard ground I at once took three measures for protection. I used my stick on the steps, and broke my fall a little I tilted my body to the left side, and dropping the stick extended my arms I fell rather heavily on my left side, with no other injury than a bruise over my left great trochanter Presently I got up, and went into the hotel to give a friendly warning to the proprietor I then came out to resume my walk and found the mat already removed !

Constant practice, plus a very rapid reaction-time, enabled me to convert what might have been a nasty accident into a negligible mishap

I had, perforce, to bestow some thought on the analysis of my defective walking The general weakness of my legs very quickly improved, but I was never able to regain good power in flexing my hips and so had a shuffling gait, especially in my right leg which had a slight drop foot as Sir Percy had prophesied But my main defect was spasm of the muscles of the lower part of my back, and the posterior muscles of the back of my leg, which slowed all the movements I never could clearly understand why the voluntary impulse from my brain should be not just weakened, but distorted or diverted so that my legs refused to do what I told them

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* Bird-Parliament, by Edward Fitzgerald

SLEEP

As soon as movement returned to my legs, I began to be troubled with nocturnal jerks, keeping me from getting to sleep and awaking me from deep sleep The simple and obvious remedy was sedative drugs My night nurse and I discovered a much better way

We found that the chief cause was too hot feet It cannot have been easy to find this out, as I had lost the sensation of heat and cold as far up as the ankle. By cooling the feet and sometimes the legs, I got to sleep, only to be wakened in $^1/_2$–$1^1/_2$ hours by kicking legs The nurse would then cool the feet or legs and turn me over and I would go to sleep at once. This would be repeated at least six times each night, and yet I would get a good allowance of refreshing sleep

Sedatives or tranquillisers should not be used as symptomatic treatment until an intelligent effort has been made to discover and to remove the exciting cause Such drugs are not good for morale The jerks have continued for thirty years, and have never required treatment with drugs

THE RETURN TO WORK

It was my full intention to return to my work as surgeon before the end of the year, but, as the hospital committee did not understand that this was possible, I was asked to go for review to London, as suggested by Sir Percy Sargent. The late Dr George Riddoch, whose work on injuries of the spinal cord during the first world war made him the acknowledged expert on this subject, gave his verdict in the beginning of December " You must return to work on Jan 1 This is not a piece of advice, it is an order You will, so far as your disability is concerned, soon be equal to your full work, and will be able to complete your full term as surgeon to the Royal Infirmary " This clear definite verdict, remarkable for its accuracy and its clinical acumen, was most valuable to me and enabled me to meet with full confidence all the difficulties that face the disabled man on his return to active life. For my part, although I had had considerable acquaintance during more than twenty-five years with the Workmen's Compensation Act of that day, it was not until I faced the problems of my own return to work that I fully realised the many hardships and often the unhappiness and anxiety that the disabled workman had to endure

MY DOCTORS AND NURSES

Since the above verdict, I never had a doctor (save for two minor incidents) during the next twenty-five years The explanation was simple In 1930, the treatment of paralysis, especially the spinal type, was neglected It would have been difficult at that time to find a doctor who would have believed in my recovery or could have helped me This had one great compensating advantage It left me free to live my own life, not under doctor's orders, to carry out my full duties as surgeon and as citizen, to drive my car, to golf, to walk the moors, to climb—in short to live the full joyous happy life, with the spice of adventure in addition.

My nurses were wonderful they had worked with me, now they cared for me. In particular they saved me from bedsores, no small feat. They went about their work with the ease and grace which attend competence and experience Associated with them was one, not herself a nurse, who devoted to me an unwearying care, a courage and initiative, and a sound practical common sense, without which my recovery would have been quite impossible—my wife. My sickroom was a happy place. A good nurse makes a good patient

THE URÆMIC EPISODE

About the age of 73 my health began to fail. The symptoms of uræmia were atypical, and the urinary symptoms masked because of the automatic bladder After about three years I became disinclined to walk ceased to perspire, was thirsty, ate poorly, and lost weight. I was advised to have my blood-urea taken It was 64 and was passed as high normal About two months later, after a short tour to Scotland, it was 138 I disbelieved this, because I had never had any headache and could still drive my car 200 miles in a day A fortnight later it was 158, and I was given an ultimatum I was ill-suited for operation. My skin was in a poor state, an old scar had broken down and refused to heal my bladder was chronically infected, at operation the bladder which for years had been contracted, with very thick wall and a maximum content of 6 oz , was found to contain 40 oz of retained urine Under local anæsthesia, with all precautions, a suprapubic cystostomy was performed. My blood-urea a week later was 120 The operation has achieved the maximum of success At the present time, more than two years later, I am well and independent My bladder drains through the permanent suprapubic opening, by means of a self-retaining Foley catheter, which I change myself every six weeks The wound and the tube channel are healed There is no leakage and no discharge and I wear no dressing or belt. For years I have worn an appliance for the prevention of double inguinal hernia, and to this my bag by day and my tube by night are fixed. I have no urinary symptoms whatever For this excellent result of an operation which has not a good reputation, I owe a great debt to my surgeon There was no emotional reaction, nor any occasion therefor A good surgeon makes a good patient

THE SETBACK

This was the great surprise of my life I was convinced that my spinal lesion was quiescent after twenty-nine years The way in which it flared up is perhaps worth describing in detail

On Monday, July 27, 1959, returning home after a frugal lunch, I felt sleepy and sat down on an easy chair, my legs supported from knee to foot on another chair When I awoke, I could not move my left leg After waiting a few minutes, I managed to struggle to my feet, and, with the aid of my stick and the furniture, to reach the hall. There my left foot trailed and I fell I pulled myself up by means of a chair, and in about ten minutes the left leg returned to normal. I walked quite normally round the lawn to the summerhouse as I stood beside it my left leg suddenly lost all its power and I nearly fell. I then, after a minute, was able to walk normally into the house, when suddenly it failed again for a minute Thereafter, for three complete days I was in my usual health—motoring, walking, and going round a hospital On retiring to bed after three days I found that both legs had lost power to a serious degree The next morning I could just dress and attend to myself, and walk with short shuffling footsteps and trailing left leg, aided by my stick, across the lawn. The old spasticity in my back had returned.

I slowly improved but after three weeks my legs were completely fatigued after 100 yards After three to four months I had steadily returned nearly to my old state of health My whole technique as regards movement had to be delicately readjusted I can again walk slowly as far as $^{1}/_{2}$–1 mile in a day, drive the car with ease and freedom, but am more spastic than I was I have still no idea of the cause of this setback

SUMMING-UP

This simple tale shows the unity of the human organism, body, spirit, and mind This illness, a paralysis, might have been regarded as purely physical The record shows that it excited powerful emotional reactions The emotions were diverted from their normal outlet into channels of purposive activity They stimulated the intelligence, so that the spirit and the mind, acting together, dominated the body, and raised it to the highest level that the remaining disabilities would permit At this level, body, mind, and spirit acted in as perfect unison as in the healthy human being

There are few who would go so far as Plato and wish their doctor to have many illnesses, but this tale supports Plato's thesis that a doctor who has an illness learns the better to understand his patient's feelings and acquires a deeper understanding of his art

X.Y Z

The Widdicombe File

LVIII.—HEARTBREAK HOSPITAL

Dear Jack,

It was good of you to send us a Christmas card, early as always, and a very merry Christmas to you, too, and to your staff, God bless them! It was in their position in that very hospital (as you probably well know) that I spent my first Christmas as a junior resident, for my sins, and whatever sins I may have had—and they were many —I reckon I just about got up to date with them there That, of course, was before they made you the Surgeon, so doubtless times have changed It was a shattering experience which haunts me still, and I'm thankful that my physical stamina (carefully nurtured by six years' studious neglect of work) got me through Let me tell you about it I need to get it out of my system

It's really not so long ago that I found myself at that loosest of loose ends where you've got no prospect of employment the next month but the mortgage has to be paid Thus it was that my desperate postal pleas reached your St Beezum's Hospital—lately the Wapchester Municipal Institution, or, as it was familiarly called, the Golden Gates of Wapchester Faltering steps led me to a great grey gaunt building, rising, all slate and dirty brick and crowned by the regulation water-tower, from a sea of monotonous black slum roofs It was enfortressed from the surroundings (? to keep the patients in) by a huge wall and gates of immense size In response to my tinklings a gloomy porter creaked them open and led me solemnly over courtyards of decaying asphalt and sterile flowerbeds and by great blocks of seemingly deserted wards—somewhat after the manner of the boatman conveying the souls of the dead across the river Styx He left me at last, alone in the residents' mess to take in a further dismal scene The room was decorated in old dark-green paint and crammed with heavy Victorian furniture a decrepit sideboard contained some battered cutlery, mats, cruet, an empty jar of piccalilli, and yesterday's *Mirror* A vast bookcase housed a few tattered *Lancets*, the Calcutta Review of Public Health for 1947, the front and back covers of *The History of the War in Pictures*, and *Anna Karenina* missing pp 638–921 There was also an empty beer-bottle and, for some inexplicable reason, volumes of the *London Companion* for 1862 to 1875, bound neatly in leather A torn and tea-stained cloth covered the table, and there were neither pictures nor fire The clock had stopped at 7 23, and the room seemed to be lit by a 10-watt bulb It seemed impossible that anyone could actually be *living* there—even the flies were dead I turned on an elderly radio—some relic apparently of early electronic history, but the only thing I got was a strong smell of burning A crone hobbled out of the nether regions "'Ere, can't use that, it's busted" She examined me more closely "You the new doctor? Didn't tell me you was coming they didn't, ain't got yer room ready" With which hearty greeting she disappeared into the ground

This is just the introduction, setting the scene for you, but perhaps you would be bored by all the dreadful detail—the great cold bedroom on the third floor against which a diminutive gas fire battled valiantly but in vain —the awful plumbing noises and the trains that kept me awake on the rare occasions when patients didn't—the complete lack of recreational amenities apart from the nursing staff (not that we had time)—the food, oh the food, words fail me, ghastly hashed-up reheated slosh, armour-plated fried eggs, pastry like cardboard—the endless bickering with the hospital secretary which never got us anything but promises—and the hours! Half-day a week and one weekend in three gave me about a 140-hour week, and, with salaries then £350 less £100 for the appalling living quarters that I had no desire whatever to inhabit, I was being paid at about 8½*d* an hour I suppose it was terribly good clinical experience that I shall always be grateful for and all that, but it didn't strike me that way at the time I should really have quit, I suppose, but one is very green and insecure round about the time of qualifying, and generally frightened of everybody My maturer colleagues in the mess might have made a fuss, but being largely foreign they were uncertain of themselves too It was, as you know, a busy hospital, and with two wards of 54 beds, mostly acute, I had enough to do The prospect of reading up one's cases or studying for an exam was a quite laughable one

You don't need to tell me that since then the place has been redecorated—they started before I left But those old buildings need a lot more than the odd coat of paint The coke boilers of circa 1875 won't usually stand the extra basins and radiators that make such a difference when the cold north-easter blows over the Pennines at this time of year I know, too, that teaching hospitals often offer an even rawer deal to their young chaps, secure in the knowledge that the supply of eager applicants is unquenchable It has been said, also, that your junior staff are now more numerous and that a television set will probably make their Christmas vigil a happier one, but I wonder! Is it true that you had no applications for your last H S vacancy apart from an M D (Skorblensk) of 58, reinstated by the G M C last year after a number of drug offences? If this is true (and somehow I hope it is) it might make that dreary old committee of yours see the red light and do something at last. Married quarters would solve your problem, even if it did mean more building. A really solid staff shortage is the only thing, in my experience, to shift a lay committee—which is probably why so many dull old hospitals have such pleasant new nurses' homes.

Let's face it Jack, junior staff have a pretty bad time of it. Not so bad as in our day perhaps, but the increase in salary has scarcely kept up with the cost of living, and the hours, even now, are often atrocious. They don't usually know their rights (have your administrators shown the juniors the Ministry circular on Standards of Accommodation H.M.58/68—have they? I bet!), and when they do they are too insecure and scared to make a fuss. And not without reason, for it may be professional death to become known as a "trouble-maker." I wonder if your medical committee has a junior staff representative yet? This proposal has been approved by quite exalted bodies—although often the behaviour of consultants at this function is far too disturbed to exhibit before junior gaze. However, a junior's presence is to be encouraged, if only to make his seniors act like gentlemen. One of our splendid representative bodies, not a hundred miles from Tavistock Square, is at present trying to compose a sort of *Guide Michelin* to hospitals in the N.H.S., and good luck to it. The trouble seems to be that the questionary is not getting through to the very chaps that should be filling it in: our region held a meeting not long ago and none of the junior staff there had heard of it. It's a modest affair concerned with matters of solid fact—none of the 5-star business yet—but I hope the next edition will be more enterprising. Good luck to it anyway, it is contributing, if meagrely, to the Millennium.

So a Happy Christmas to you Jack—and to your staff. Spare a thought for them as you carve the turkey in the bosom of your family on Christmas day, on Christmas day, on Christmas day in the morning.

Your old and affectionate friend,
RICHARD COBBLEIGH.

Public Health

The Registrar-General's Commentary

IN his commentary on the statistics for England and Wales for 1957[1] the Registrar General remarks that the home population has been increasing by an average of 180,000 a year, in round numbers, since 1951, and in the twelve months mid-1956 to mid-1957 it increased by 240,000 to an estimated 44,907,000.

The "natural increase" (the excess of births over deaths) was 226,000 in 1956–57—a year of high birth-rate and low mortality. About 106 boys are born for every 100 girls, but the death-rates for males are higher than those for females at all ages, so at ages 0–4 there were 1053 males per 1000 females, at ages 30–34 the numbers were about equal, at ages 60–64 there were 770 males per 1000 females, and at ages 75 and over there were nearly twice as many women as men.

Births.—The 723,381 live births in 1957 were the largest number since 1949, and the birth-rate of 16·1 per 1000 population was the highest since 1950. This increase continued the upward trend which began in the late spring of 1955. (The 1958 rate was higher still, at 16·4.)

Marriages.—There were 346,903 marriages in 1957—6000 fewer than in 1956. The decrease was due to the smaller number of unmarried persons of marriageable age in the population. The marriage-rate—15·4 persons marrying per 1000 total population—was slightly lower than in 1956. The tendency to younger marriage is reflected in the proportion of grooms and brides who are under 21. For men it rose from 3·4% in 1938 to 8·7% in 1956 and to 9·6% in 1957, for women from 16·4% in 1938 to 32·2% and 33·6% in 1956 and 1957.

Deaths.—There were 514,870 deaths registered in 1957, the death-rate for both sexes being slightly lower than in 1956.

Infant mortality and stillbirths.—The infant-mortality rate was 23·1 per 1000 live births in 1957, and was the lowest recorded in England and Wales (the 1958 rate was lower still, at 22·5). More than 60% of the deaths occurred in the first week of life, but the rate for these deaths in the first week (14·1) was also the lowest recorded in this country. The stillbirth-rate of 22·5 per 1000 total live and still births was slightly lower than in 1956. Immaturity continued to be the chief cause of infant mortality.

Tuberculosis.—There were 4784 deaths from tuberculosis in 1957—11% less than in 1956. Deaths from respiratory tuberculosis fell by 12%, but for the first time for many years there was a small rise in the number of deaths from the non-respiratory form—from 522 in 1956 to 535 in 1957. There were no deaths from respiratory tuberculosis of boys aged 5–9 or of girls aged 10–14. Notification-rates continued to decrease, being 82 per 100,000 population for males and 49 for females. Mass miniature radiography units made 3,514,600 examinations in 1957; the number of cases found by these units was 22% of all cases of respiratory tuberculosis notified. The highest incidence of cases was again found among persons referred to the units by general practitioners.

Cancer.—Deaths assigned to cancer in 1957 numbered 94,017 (50,056 male and 43,961 female), the highest numbers yet recorded. The largest increase in cancer mortality in both sexes since 1936–39 has been from cancer of the lung. Cancer of the lung accounted for the highest proportion (nearly a third) of all male deaths from cancer in 1957 and for about 6% of all female deaths from cancer.

Diseases of the circulatory system.—In 1957 there were 188,630 deaths assigned to diseases of the circulatory system and a further 73,669 to vascular lesions of the central nervous system, which together accounted for 51% of all deaths.

Accidental and violent deaths.—There was a decrease in 1957 in the number of deaths due to accidents and violence, which numbered 21,561 compared with 21,870 in 1956.

Registration of Food Premises

In his annual report for 1958, Dr J. H. Briscoe-Smith, medical officer of health for St. Marylebone, describes a sharp outbreak of food-poisoning, involving two schools, in which 62 pupils and staff were affected. The cases were spread over seventeen local-authority areas, and, apart from verbal notification of the original case, only 3 cases were notified. Had this outbreak resulted from consumption of food in a restaurant it might have remained undetected or, at best, investigation might have linked the 4 notified cases.

> "the control of detected cases of food-poisoning and their contacts, though essential, is much less likely to be effective than a direct attack on the source of the infection by the close supervision of every place where food is produced, prepared, handled or eaten to ensure that every precaution is taken against its contamination.
> The registration of all food premises is long overdue and it is a sad commentary on the present state of the law that while one shopkeeper selling packaged ice-cream from a refrigerator is required to register with the local authority, his next door neighbour selling frozen foods is not required to do so. Many of these foods such as made up meat and fish dishes, some of which may be prepared as far afield as Italy, are, if not stored properly, potentially at least as dangerous as ice-cream and are much more liable to contamination during manufacture.'

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[1] The Registrar General's Statistical Review for England and Wales, 1957, Part III, Commentary. H.M. Stationery Office. 1959. Pp. 299. 16s. 6d.

In England Now

A Running Commentary by Peripatetic Correspondents

IT is an unhappy Christmas Day tradition in most hospitals for the senior surgeon to carve the ward turkey, usually with a display of ill-concealed inaptitude both anorexigenic and alarming to any patient about to undergo surgery It is also customary to cast the pædiatrician in the role of Father Christmas at the children's party and this, too, is an unsatisfactory arrangement.

To begin with, the disguise is hot and uncomfortable One frequently trips over bits of trailing robe, and wisps of cotton wool have a propensity for invading oto-oro-rhinological orifices with irritating consequences which may render inadequate control over blasphemous interjection. For a few children the appearance of Father Christmas is the signal for a prolonged and piercing howl, unappeased by a chorus of a dozen shameless brats to the effect that "He's not Father Christmas at all, but that nasty doctor who gave us the needle the other day!"

Having restored some semblance of order (a semblance being all that is ever feasible on these occasions), one must then begin the dangerous business of distributing the presents The opening of the first parcel is the cue for a mad onrush of hordes of small children and, notwithstanding a bodyguard of stalwart nurses, the little horrors are liable to swamp trees, parcels, presents, Father Christmas, and everything It is an unfortunate trend of our times to provide children with all manner of warring implements, and Father Christmas at once becomes the ready target for a variety of missiles ejected from crossbows, pop-guns, catapults, water-pistols, and so on Some of the little devils are so preoccupied with fighting that they fail to answer when their names are called Then, every now and again, some juvenile impostor will claim a parcel destined for someone else, who soon raises a vociferous condemnation of this outrage To mete out justice under these circumstances merely serves to transfer noise from one source to another A final difficulty, for which there is no remedy, is that some child has to have his present last of all A prolonged wait does nothing to enhance appreciation Either he has one like it already only better, or it is the wrong colour, shape, or size, or perhaps neighbouring destructive influences are brought to bear at an early stage

Thank heaven I have seen the last of Christmas for the next twelve months

* * *

I have already spent a fortnight in bed with influenza, but I am glad to stay in for a few more days, for the weather is terrible A gale with slush and snow is blowing and everything is in disorder, because every year the winter comes as a great surprise to this country The papers are full of descriptions of 300 cars in one big mass on the main road to Copenhagen All the trains are stuck at Glostrup because the signals are frozen. The ferry from Elsinore to Halsingborg cannot carry the international sleeping-cars, because they are too heavy and the ferry will tip over in the wind And a woman in Busserup had her child before the midwife arrived, late in the snow

All this makes soothing reading when you are in bed and have time to read Professor Blackett's article in the *New Statesman* I think it's time Britain and Denmark and other countries stopped making or buying atom bombs and concentrated on getting a bit of gravel on the roads to help the midwife to get to Busserup in time

* * *

Thirty years ago, my straw hat and a noisy packet of crisps held in a sweating hand, with boils on my neck, I was impelled on and down, down into the pit (*9d*) by sex, a dirty word in those days, by posters declaiming "The Eternal Eve" I huddled into the plush seat thankfully No prefect had spotted me Through the miasma of the years I still recall the pervasive smell of patchouli, those gorgeous stark Dietrich legs, the insolent heavy-lidded vulpine stare, and the soul-freezing stuff that only U F A *Studios* could produce—"Kiss me, my fool" My heart bled for poor dear old Emil Jannings, haggard and humiliated, even for his fatuous *furor teutonicus* and the universal and grimy Weltschmerz

Last week my children took me to *The Blue Angel* and we sat in pseudo zebra-skin tip-ups, through a pervasive smell of Heavenly Mist But the saucy tone-deaf child-siren with flaring nostrils and android hips had little to offer, even with her race-horse legs thrown in. My sour heart did not thrombose over the agitated and vulgar domestic peccadilloes The film was all too evilly refined and morbidly tiresome Yet as the lights went up a lad with boils on his neck and a straw hat in his hand hurried out I thought he looked like any other boy, but my children said he looked rather like me

* * *

Routine laboratory work may appear dull and humdrum, but it has its rewarding moments

The young, newly promoted student technician in blood-transfusion had laboriously completed his first routine examination of samples of blood from the antenatal clinic. The ABO groups agreed, the Rh⁻ groups, using two different anti-D sera, agreed, and the antibody tests were also in agreement The long afternoon session was at an end most satisfactorily I turned to him and said, "That's wonderful" He sighed and, with heightened colour and sparkling eye, he replied, "It's not wonderful, it's a ruddy miracle"

* * *

Americans are an oral nation and no mistake As part of the universal milk-and-honey, there is an immense proliferation of candy, milk-bars, chewing-gum, and cigars What with Hollywood, teenagers, and baby-dolls, kissing has become the major industry and a prime raw material for export But alas! cigarettes are already under sentence, cranberries are suspect, and now another subtle blight has fallen on the unhappy land. Long-suffering rats, painted year by patient year with lipstick dyes, have at last developed tumours Suddenly the American skies, the biggest and bluest ever, are darkened Lipstick is out, goodbye glamour Whatever will be the effect of it all? The women's strike fomented by that arch-shop-steward Lysistrata averted war, certainly, but probably only because the men were too busy arguing with their wives to fight the enemy What will happen now that oral aggression can no longer take its rightful avenue? Shall we see a bitter outburst of frustrated verbal savagery and a renewal of international discord, or will there merely be a boom in American milk-sales?

* * *

CHRISTMAS NIGHT IN THE DOGHOUSE

Nowell, nowell, nowell, nowell!
That may be what *you* say—I say what the hell
You say, Christmas comes but *once* a year—
What do you expect me to do about it? Cheer?
And if you do, for precisely that reason
I hereby resolve to scrub round all compliments of the season
Of robins giblets and fetch your own blooming log
As well as of all pushing characters with something to flog
As the commercial buildup gets huger and huger
Personally this person gets Scrooger and Scrooger
So resisting all those spiels
With hark the herald thank you Sirs and sticky seals
Let them, I say, decorate their tents prefabs and baronial halls
With luminous glass bodgers and little balls—
At the sight of a cracker tears
Run down my nose for all you victims of racketeers
And when I think about the lolly
Spivs make annually out of the craving for holly
Anyone who in my hearing mentions Bob Crachitt
Is going to catch it
    Hark the Herald Angels sing
      Gramophones and plastic string
    Rheum and reindeer, crackling, carols,
      Slipping discs, and rolling barrels
    Gourmandising grub and culture,
      Christmas hastens our sepulture—
    May you at this festive season
      Get the chance to name your poison

Letters to the Editor

USE OF THE TERM "SUPERFEMALE"

SIR,—I hope that nothing I say will be regarded as any eflection on the importance of Jacobs et al 's[1] demonstration of the existence of an XXX chromosome pattern in a woman with hypoplastic genitalia, but I must own to a certain satisfaction on seeing Dr Stern[2] cast doubt on the propriety of the name "superfemale" Though their letter of Dec 19 answers part of Dr Stern's objections on genetic grounds, I think from a more general point of view t is possible to criticise "superfemale" This name has he important advantages of being memorable and being napplicable to any other syndrome, but it is frankly miseading as a clinical description Moreover, it has an emotional element which should be avoided, if possible, in he terms we use in speaking of patients with this kind of disorder Dr Stern's alternative of "metafemale" avoids he positive error but falls into the opposite one of vagueness there is a large class of cases to which the term metafemale could be applied (all the varieties of female pseudohermaphroditism, for instance) and only arbitrary definition can confine it to the sense he proposes

Surely there is a far simpler solution in the use of the chromosome constitution as part of the name? The chromosome constitution is the best definition of the syndrome, and it could simply be called the "XXX syndrome" One could similarly resolve arguments as to the names of other syndromes with chromosomal anomalies If one introduces the XXY into the name of what I used to call chromatin-positive Klinefelter's syndrome, there can be no ambiguity as to what one is talking about The "XXY syndrome" would suffice, though most people will probably prefer to use "XXY Klinefelter's syndrome" or some such phrase The Turner's syndrome complex is more difficult, simply because it is a complex, but if the results of Harnden and Stewart[3] prove to be generally applicable, it may well turn out to be justifiable to speak of "XO Turner's syndrome" for the classical cases and "XY gonadal dysgenesis" for the cases without stigmata Mongolism might well be called "22-trisomy" if we are to carry this out logically—though here, of course, we are handicapped by the absence of an agreed nomenclature for any of the chromosomes except the sex chromosomes

As Ben Jonson so wisely said, "A man coynes not a new word without some perill, and lesse fruit, for if it happen to be received, the praise is but moderate, if refus'd, the scorne is assur'd Yet wee must adventure" It *may* be premature to use chromosome constitution in definition and naming But the advantages would be great, and the risk I think slight "Wee must adventure"!

Department of Pathology,
Western Infirmary,
Glasgow

BERNARD LENNOX

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—I have read many papers like that of Dr Simpson (Dec 12) advocating that cavernous hæmangiomata should be given "expectant treatment", that pompous locution for doing nothing None of them brings out two important points The first is that many dreadful disfigurements, particularly of the face, begin as tiny red spots, either present at birth or appearing in the first month Nobody knows what would happen if they were efficiently treated at this stage, since they are quite invariably dismissed as trivialities, it would be interesting to find out

In spite of preaching for years that a growing red spot on a baby s face is a surgical emergency, I have never yet had one referred to me at this stage by a general practitioner, but I have picked up a few and treated them The results suggest that the process of regression can be started very early in the growing stage by producing inflammation in the abnormal tissues

The second point is what happens to the cases which disappear from these inquiries It is undeniable that many mothers, in horror at what is happening to their babies' faces, seek the aid of surgery It would be interesting to know how many

London, W 1

DENIS BROWNE

SIR,—I read with interest Dr Simpson's article of Dec 12 It only goes to prove how misleading statistics can be, and what large numbers must be studied

All are agreed that cavernous angiomas disappear in the course of time, but they are likely to leave atrophic depigmented areas, not infrequently they undergo spontaneous ulceration which results in a cure, but the resulting scar is apt to be disfiguring

I should like to quote from a paper by Andrews et al[1]

> ' The records of 1113 patients with angioma who were observed at the Columbia University-Presbyterian Medical Center between 1932 and 1955 were studied Of these, 320 had hemangioma simplex and 584 had hemangioma cavernosum Of the 153 patients with hemangioma simplex who received no treatment, 102 could be observed adequately The lesions of 64 (63%) involuted or improved within 5 years, whereas those of the other 38 (37%) persisted after 5 years Of the hemangiomas simplex which involuted spontaneously, 83% were 1 cm or less in diameter It may be concluded that any hemangioma simplex on the face measuring 1 cm or more should be treated promptly, since it is unlikely to undergo involution without therapy The danger of ulceration of hemangiomas on the lips, nostrils, eyelids and ears suggests that these should be treated even though less than 1 cm in diameter
>
> " Of the cavernous hemangiomas of 135 patients who received no treatment during the first 5 years of life and who could be followed adequately, 22 (16%) involuted or improved within 5 years The lesions of 113 (84%) persisted more than 5 years This high percentage indicates the desirability of treatment for all cavernous hemangiomas '

I think there is a great tendency to exaggerate the frequency with which congenital hæmangiomata undergo spontaneous involution and disappearance

I should also like to refer to a paper that Dr E Millington, radiotherapist at the Royal Sussex County Hospital, and I read at the Brighton and Sussex Medico-Chirurgical Society in 1953

> In a survey made at the various hospitals in Sussex and Kent of 1752 cases of angiomas, 814 received X-ray therapy, the criterion of recovery being the maternal satisfaction in all cases The treatment consisted of one, two, or three treatments of 400–600r repeated at 6-monthly intervals 200 cases in the series required treatment after the 5-year period, and only 20% cleared in the first year In a personal communication, Professor Trueman-Nelson confirmed the view borne out by these results
>
> The series by J Walter, of Sheffield, comparing 83 untreated cases with 88 treated was too small By choosing an equal number of patients at various periods in our group these figures could be confirmed and contradicted

The late Dr Roxburgh believed that although a large number of cavernous nævi show a marked increase in size in the first 6 months of life, they usually disappeared spontaneously, but there is another less common type, quite indistinguishable, which tends to increase in size, but does not disappear at the 5th year, and indeed often increases in size at this age

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[1] Jacobs P A, Baikie A G, Court Brown W M MacGregor T N, Maclean H, Harnden D G *Lancet* 1959, ii 423
[2] Stern C *ibid* p 1088
[3] Harnden D G, Stewart, J S S *Brit med J* 1959 ii 1285

[1] Andrews, G C Domonkos, A N Torres-Rodriguez, V M, Bembenista J K *J Amer med Ass* 1957, 165, 1114

If cavernous hæmangiomata are alleged to clear spontaneously how is it that so many are met in adult life?

Hove, Sussex E COLIN-JONES

INTRATHECAL PHENOL AND RELIEF OF SPASTICITY

SIR,—I wonder if I might be permitted to make a few comments on the papers by Dr Nathan and by Dr Kelly and Dr Gautier-Smith in your issue of Dec 19

Dr Nathan and Dr Kelly will, I am sure, recall that Dr Maher and I have long been interested in this particular manœuvre, for they contributed in a very agreeable and informed way to the discussion on a paper which I gave on this subject in April, 1959 Perhaps I might add that Dr Maher and I at this very moment have a paper on our experiences with this technique in the hands of the Editor of another journal

The earliest occasion in which we used this technique was in the case of a patient with a hemiplegia who was treated by Dr Maher in April, 1956, and it is quite satisfying to report that this patient is still ambulant in December, 1959 Another patient with multiple sclerosis and painful flexor spasms which made sleep impossible for her was first treated in November, 1957, and again in January, 1959, because of recurrence of the spasms This accords with the experience of Dr Nathan and Dr Kelly, who had both found that reinjection proved very helpful

We are all well aware of the disadvantages of the method I was interested to note that Dr Nathan mentions the danger of paralysing the sphincters Our experience has been that the most probable affection of bladder function is that of retention, cystometrograms in such cases have demonstrated that the bladder muscle is atonic but the sphincter is not paralysed A short period of tidal irrigation has resulted in recovery of bladder function within the space of three to four weeks in most cases of this nature, but in one of them it was necessary to resort to bladder-neck resection (Mr T Moore)

Dr Kelly finds that phenol in myodil is more satisfactory, but our experience has been that its effect is of relatively short duration, and the use of this particular combination seems to interfere to some extent with the later effect of phenol in glycerin One has the impression that the deposition of the myodil solution round the nerve-roots in some way prevents subsequent use of phenol in glycerin from producing its full effect We have used the glycerin solution in ambulant patients, but our practice is to try 2% rather than 5% solution in such cases, in order to avoid diminution of motor power

Although Dr Nathan has found little change in the constitution of the C S F following the introduction of phenol into the theca, we have found that the protein in certain cases may rise as high as 400 mg per 100 ml, but, as he says, the meningeal response is surprisingly mild

One point of philosophical interest emerges One gathers that Dr Nathan and Dr Kelly were carrying out their clinical experiments simultaneously with our work, although they do not mention any precise dates of the cases which they describe in detail It seems that this is yet another example of the creative urge of the Zeitgeist

Department of Neurology,
The Royal Infirmary,
Manchester L A LIVERSEDGE

SIR,—The two articles on intrathecal phenol follow closely the experience in this unit, where the original Maher technique has been used and spasms have been relieved satisfactorily

Dr Nathan pools his solution at the anterior root. Dr Kelly and Dr Gautier-Smith have their patient in the lateral position, which would presumably affect both roots, but more the posterior one In a short series of mine the posterior roots have mainly been affected These differing methods have all produced relief of spasms, though it would appear that Dr Nathan's method gives a more permanent result, and this must be due to his concentrating on the anterior root In the future I think this will prove to be the method of choice in most cases, but it may well be that in those patients where an attempt should be made to conserve residual voluntary movement, a relatively " weak " phenol solution concentrated mainly on the posterior root would be best If this failed a strong solution could always be used later, on the anterior root.

The following two cases are of interest The first because of a considerable recovery of voluntary power, the second because it involved the treatment of a spastic arm

(1) A woman with cervical spondylosis and bilateral severe flexion and adduction spasticity of the legs with flexor spasms A number of intrathecal blocks relieved the spasms and unmasked enough voluntary movement and power in one leg to allow her to push herself up the bed when she slid down

(2) A young man with spasticity of arm and leg after a head injury (no spasms) His fingers were digging into the palm of his hand and producing pressure sores 3 ml. phenol (1 15 in glycerin) at the cervical level relieved the spasticity and uncovered voluntary movement of the hand He then had a weak but very useful grip

Finally, two questions One to Dr Nathan, who mentioned the danger of paralysing the bladder sphincters has he had any complications of this nature in his series and if so to what degree? The other to Dr Kelly and Dr Gautier-Smith it would be valuable to know their criteria for deciding what concentration of phenol to use (the range 5–20% is rather large)

I found the two articles of great interest and much value

Regional Neurosurgical Centre,
Liverpool S LIPTON

THE CONVALESCENT EXCRETER OF SALMONELLÆ

SIR,—In a recent annotation[1] on the treatment of salmonella carriers, you discussed the possible value of furazolidone (' Furoxone ') At that time only one clinical paper[2] dealing with this drug had been published Since then more articles have appeared[3–6] These reports are concerned with the treatment of a total of 271 patients, of which 255 became symptom-free after three to five days' therapy with furazolidone 105 were shown to be suffering from infections with one or more strains of the following organisms shigella, salmonella, escherichia, staphylococcus, streptococcus, giardia, entamœba, and proteus

4 patients who were suffering from *Shigella sonnei* infections were not cured by chloramphenicol After subsequent treatment with furazolidone a clinical and bacteriological cure was obtained *In addition, the patients with the protozoal*

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1 *Lancet*, 1959, ii, 501
2 Ponce de Leon, E *Antibiot Med* 1957, 4 814
3 Baddeley, H, Baird, T, Fletcher, F *Med Pr* 1959, 242, 172
4 Turnbull, T A *Med Proc S Afr* 1959, 5, 423
5 Nassa, A *Brit med J* 1959, ii, 1063
6 Rettig, J H Scientific Exhibit, American Medical Association Meeting, Atlantic City, 1959

infections (11 in number) also became symptom-free and showed negative stool-cultures after therapy In all of these investigations no side-effects other than very occasional nausea and vomiting were experienced.

Your annotation also referred to the treatment of *Salmonella typhimurium* infections in fowls with furazolidone, and it was stated that most of the birds which survived became chronic "carriers". In human gastrointestinal infections, however, this has not been shown to occur, few patients continued to carry this, or other pathogens, after treatment.

The presence of pathogenic organisms in the stools was demonstrated in 105 patients After treatment, 97 showed negative stool-cultures, but the remaining 8 continued to harbour pathogens

The only work on the treatment of carrier states is by Hobson,[7] who investigated the action of furazolidone in mice made "carriers" of *S typhimurium* Treatment with high doses of this drug freed 8 out of 16 mice from this organism. In another group of 16 such carriers that received no treatment, only 1 mouse freed itself spontaneously from the pathogen.

Smith Kline & French Laboratories,
Welwyn Garden City, Herts

I SCHRIRE

TREATMENT OF BLEEDING PEPTIC ULCER

SIR,—In reply to Dr Koster (Dec 26) may I say that

(1) Operation is indicated if the patient has renewed massive bleeding after admission to the hospital or if such a condition continues after admission Massive bleeding is a condition where it is impossible to keep the blood-pressure normal without continued transfusion.

(2) The age of the 6 patients who died unoperated upon was between 70 and 92 3 patients had such a severe cardiac insufficiency that operative treatment was presumed contra-indicated for they could not even be transfused. 2 patients died in the first two hours after admission despite transfusion. Because of his age, the patient of 92 years was not operated on although he did have renewed bleeding

Drammen, Norway

OLAF ROMCKE

SIR,—I should like to support Mr Lytton's remarks (Dec 26) concerning patients with melæna, but without hæmatemesis, and in whom no diagnosis is made

An identical case to Mr Lytton's was treated in this hospital in 1957, and another stomach was lost needlessly, the bleeding coming from a small hæmangioma about 0 5 cm in diameter, involving the anti-mesenteric border of the jejunum about 4 feet from the duodenojejunal flexure

This man, aged 45, was admitted in November, 1957, with a severe attack of melæna of 3 days' duration, with no associated dyspepsia Transfusion was undertaken, but further heavy melæna produced unconsciousness which recovered with subsequent rapid transfusion.

At laparotomy on Dec. 15 no abnormality was found, but the jejunum and ileum were full of blood. A blind partial gastrectomy was undertaken, but the bleeding continued and it was decided to undertake a further laparotomy on Dec. 20 On this occasion there was blood only in the ileum, and a small jejunal lesion was indicated by a leash of vessels running towards the acute mesenteric border, but no underlying thickening or ulcer could be felt Resection was undertaken and the lesion proved to be a necrotic jejunal hæmangioma.

His subsequent progress was uneventful, apart from the development of an incisional hernia, and when he was last seen several months ago his general condition was excellent.

In this case there had been a careful search of the small intestines, but the lesion was missed on the first occasion On the second occasion it was relatively easy to find the lesion as the jejunum was empty of blood.

Hackney Hospital,
London, E.9

R F READ

ORAL HYPOGLYCÆMIC AGENTS

SIR,—In your leading article of Dec 19 you wonder whether early enthusiasm has made too light of the disadvantages of these drugs, using insulin as a standard of reference. This may be so, but I feel it equally pertinent to wonder whether we are too complacent in our attitude to insulin Insulin is not satisfactory replacement therapy in diabetes, such as thyroid is in myxœdema or as cortisone is in Addison's disease. It could more closely be compared to the use of folic acid in pernicious anæmia Insulin has saved and prolonged the life of thousands of diabetics but at the same time it permits the development of the most devastating complications, even in so-called mild diabetics I have observed that some diabetics whom we have designated as "failed tablets", because while taking tablets their blood-sugars remained above normal, showed equally poor control when transferred to insulin But we were more prepared to accept hyperglycæmia in these patients on insulin, because even if the treatment were unsatisfactory, at any rate it had nearly 40 years of orthodoxy behind it. Whether hypoglycæmic agents will be more or less effective than insulin in preventing long-term complications in "mild" cases remains to be seen

There are two aspects of oral hypoglycæmic agents not treated in your leader that I feel are worthy of mention

First, in many new diabetics who initially fail to respond to diet alone but who are controlled by tablets, remission of the diabetic state occurs after normoglycæmia has been maintained for about six weeks or so If the tablets are discontinued after this length of time, in many diabetics good control continues on the same or a greater diet than was originally ineffective. In my opinion, newly diagnosed diabetics should not continue to take tablets indefinitely without establishing at some point that a remission has not taken place.

Second, since the sulphonylureas and the diguanides have a different mode of action, some diabetics who cannot achieve normoglycæmia on either preparation alone may do so on a combination. A combination of chlorpropamide and phenformin is the most effective oral hypoglycæmic therapy available today

Finally, you state that the risks of toxicity seem to be less common with chlorpropamide than with tolbutamide. I feel wider experience with chlorpropamide is necessary before this can be substantiated Sensitivity drug rashes are commoner with chlorpropamide, and whereas the therapeutic dose of tolbutamide can be exceeded with impunity, increasing the daily dose of chlorpropamide above 500 mg daily can give rise to jaundice and vertigo, suggesting a narrower margin of safety than with tolbutamide

London, W 1

ARNOLD BLOOM

DENTISTS AND ANCILLARIES

SIR,—Your annotation of Dec. 5 may lead some readers to suppose that there is a shortage of candidates for training as dentists This is not so Candidates commonly apply to three or four schools in the hope of obtaining a place at one of them The serious situation is that the number of places available annually in the United Kingdom is only about 620 although the need is for at least 900

We anxiously await the fulfilment of the Government's intention to increase the number to 890 and trust that replacement of the cramped and obsolete buildings of dental teaching hospitals will no longer be delayed.

Department of Dental Medicine,
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MARTIN A RUSHTON

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[7] Hobson, D *Brit J exp Path* 1956, 37, 20

PENICILLIN IN LEPTOSPIROSIS

SIR,—In your columns Dr Semple[1] criticised previous letters[2,3] which suggested that penicillin is of value in the treatment of leptospirosis He referred to his own article[4] in these terms " The fact remains that a properly controlled trial has been done The only way in which this can be refuted is to show some fundamental defect in the trial, or to produce contrary evidence from another equally or better controlled series "

The report of this trial contains only one detailed set of figures for scrutiny These are in the form of a scatter diagram showing the day of illness on which the treatment was started, and the day on which patients became free of signs and symptoms (which are not further defined) Analysis of this diagram (see table) shows that the control group and the group treated with penicillin did not differ significantly in the time at which treatment or observations commenced, but that the duration of signs and symptoms was significantly shorter in the penicillin group

ANALYSIS OF CLINICAL TRIAL OF PENICILLIN IN LEPTOSPIROSIS

Group	Number	Treatment	Day treatment started		Day free of signs and symptoms	
			Mean	Standard deviation	Mean	Standard deviation
A	31	Control	4 0	1 7	7 8	2 7
B	21	Penicillin	4 7 P>0 10	1 2	6 0 P<0 02	1 8

The figures calculated from this diagram do not agree with those given in table III by Dr Fairburn and Dr Semple, presumably derived from the same data There the duration of signs and symptoms for the control group is given as 10 8 days, and for the penicillin group as 9 7 days Does the ordinate in the diagram perhaps refer to duration of signs and symptoms after treatment? If so it does not say so, and in any case the figures should then be 11 8 and 10 7 days respectively This difference approaches, but does not reach, significance at the 5% level " Duration of signs and symptoms " seems a very subjective criterion on which to base an assessment, and one would like very much to study similar scatter diagrams showing total duration of fever and duration of fever after treatment

The distribution of serotypes in their control and treated groups is quite different Indeed, in more than half of the control series the infecting serotype remained unidentified The clinical severity of the diseases produced by different serotypes varies greatly It seems reasonable therefore to demand that studies of the efficiency of treatment should concern a single serotype, or that the groups compared should have a similar distribution of serotypes This is a difficult criterion to satisfy, as identification of the infecting serotype is never available until at least some weeks after the patient's admission It is, however, of interest that Dr Semple applied this criticism to the series of Mackay-Dick and Robinson,[5] but not to his own paper

It is contended, therefore, that the results reported by Dr Fairburn and Dr Semple do not justify their sweeping conclusions that " penicillin and chloramphenicol play no useful part in the treatment of uncomplicated leptospirosis in British troops in Malaya, and we suggest that these antibiotics are unlikely to be of value in the treatment of leptospirosis elsewhere ", because (i) their groups are not comparable in serotype distribution and (ii) even so, their figures can be used to support the value of penicillin if one ignores some inconsistencies in them

Clinical experience in North Queensland, supported by analysis of 264 cases,[6] is in complete agreement with the opinions of Mackay-Dick and Cook that penicillin is of value The practitioners in the area, when approached in 1953, considered that it was not justifiable to withhold treatment from patients It was not, and will not be, possible therefore to attempt a controlled clinical trial The same situation may well apply in other areas where leptospirosis is a common disease It would be most desirable that the detailed figures of the clinical trial reported by Dr Fairburn and Dr Semple should be submitted to tests of statistical significance

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Brisbane, Australia

R L DOHERTY

⁂Dr Doherty's letter was shown to Dr Semple and Dr Fairburn and their reply follows —ED L

SIR,—We should like to comment on the points raised by Dr Doherty and also to quote some of the statistical results in our controlled trial on the treatment of leptospirosis[4]

(a) The relevant symptoms and signs were recorded carefully every day on a standard chart by the same two observers The point at which they had ceased is a good guide to the length of the illness and marks the time when the patient is beginning to get up and about. These are not merely " subjective criteria " therefore

(b) Any confusion over the ordinate of the scatter diagram can be clarified by consulting the text of our article[1] under the Results section the ordinate being " the day on which the patient became free of symptoms and signs after the start of treatment " If the mean results from this diagram are added to the day treatment started (table II), then the total duration of symptoms and signs will be overestimated by one day, because there is a day of illness common to both figures We consider this is the reason for Dr Doherty's thinking the figures in table III to be incorrectly quoted

(c) Dr Doherty has shown that the time to become free of symptoms and signs from the start of treatment is significantly shorter in the penicillin group Because this does not take account of the day of the illness on which treatment was started it is not possible to assess reliably whether penicillin has shortened the total duration of the illness The first treatment day in each individual patient cannot be ignored on the grounds that there is no statistical difference between the mean day of the illness when treatment was started in the control and penicillin groups Indeed analysis of our results[4] (table III) showed that there was no significant difference between the control and penicillin groups as regards total duration of symptoms, signs and the total time to become free of both symptoms and signs (P > 0 1 in all cases)

(d) We found a similar pattern as regards the length of pyrexia We first compared the duration of fever in hospital of the penicillin and control groups—this relies solely on the day-to-day taking of the temperature and on no " subjective criteria " The mean difference between the two groups was only 1 5 days (penicillin the shorter), and this was not statistically significant (P > 0 1) By adding the days of illness before admission, and presumably then getting an estimate of the total length of fever, there is still no significant difference between the two groups (P > 0 05) There is, however, a significantly shorter period of fever after treatment, but this again does not take into account the time at which treatment was started in the illness, as in section (c) above

To sum up, our statistical results showed that penicillin did not significantly *alter the natural course of the disease* when compared with the controls and those treated with chloramphenicol Also, as pointed out in our trial[1] (table IV), even when treatment with penicillin was started early (before or on the 4th day of the illness) the average length of the illness was not shortened, in fact, the average

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1 Semple, S J G *Lancet*, 1959, ii, 289
2 Mackay-Dick, J, Robinson, J F *ibid* 1959, i, 100
3 Cook, A T *ibid*, 1959, ii 81
4 Fairburn A C, Semple, S J G *ibid* 1956, i, 13
5 Mackay-Dick J, Robinson, J F *J R Army med Cps*, 1957, 103, 186
6 Doherty, R L *Austr Ann Med* 1955, 4, 53, *ibid* 1956, 5, 23

number of days taken to become symptom-free and sign-free was greater when treatment was started early We do not, therefore, see any inconsistencies in our results and believe that it would be wrong to use Dr Doherty's analysis of our scatter diagram to support the use of penicillin in leptospirosis

(*e*) Now, as to leptospiral serotypes it is not possible to arrange an equal distribution between control and treated groups Dr Doherty feels that in a study of the efficacy of treatment there should be a similar distribution of serotypes, as he believes the clinical severity varies with the infecting serotype Trimble[7] in an analysis of 236 cases in Malaya showed that there was absolutely no correlation between clinical severity and serotype Analysis of our own results [1] also showed that the severity of the illness and the incidence of complications bore no relationship to any serotype or serogroup This, combined with the knowledge that as far as we know, all serotypes are sensitive to penicillin,[8] makes it unnecessary, even though desirable, to ensure an equal distribution between treated and control groups It does not support Dr Doherty's contention that the results of our clinical trial should be rejected because of this unequal distribution We agree, however, that it invalidates one particular criticism previously made concerning the use of controls from another time period [9] Nevertheless we still feel that in a clinical trial of treatment in leptospirosis it is desirable that controls and treated patients should be selected in a random manner and compared at approximately the same time period by the same observers—even when, as in this instance, it results in an unequal distribution of serotypes

We do not think that there is anything " sweeping " or inaccurate in our statement [4] that " penicillin and chloramphenicol play no useful part in the treatment of uncomplicated leptospirosis in British troops in Malaya " Our reasons are as follows (1) Penicillin (or any other antibiotic) has never been shown to affect the mortality of the disease nor the incidence of the complications, jaundice, oliguria, or anuria [4 10 11] (2) In our controlled trial [4] there was no significant effect of penicillin on total duration of pyrexia, symptoms, and signs as compared with the controls The mean results show that the length of illness was slightly shorter in the penicillin group The well-recognised variability of leptospirosis, common sense, and our statistical analysis suggest this a chance finding If it was real and due to penicillin it was marginal and of doubtful value, especially when balanced against the discomfort of frequent intramuscular injections over several days and the other disadvantages of massive antibiotic therapy Above all, it is in complete disagreement with the reported dramatic effects of penicillin elsewhere [12] and makes nonsense of any suggestion that controlled trials are unjustifiable in this instance

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A C Fairburn

St Thomas's Hospital Medical School,
London, S E 1
S J G Semple

THE ABNORMAL APPENDIX

Sir,—In his article of Dec 26 Mr Jewers referred to my work on this subject His thoughtful paper confirms the two conclusions at which I arrived in 1952, namely

(1) There is no such thing as the " conservative treatment " of appendicitis If one ever considers conservative treatment it is in relation to peritonitis and never to appendicitis, which is a different thing The treatment of appendicitis, when the necessary facilities are available, is to remove the appendix The only condition under which conservative treatment is logical is where the inflammation has spread beyond the appendix and peritonitis is present, the decision then for operation against conservative treatment being a nice one to be made with every ounce of the surgeon's lifetime's experience

(2) Appendix abscess is now the most dangerous of all the situations resultant on appendicular inflammation.

London, W 1
W Skyrme Rees

EVENING COLIC IN INFANTS

Sir,—Professor Illingworth's views on the management of screaming infants are of considerable importance to family doctors In his report (Dec 19) on the trial of dicyclomine hydrochloride in evening colic in infants he shows that, of the 15 babies who received active drug and inert substance, each for a week, 9 had higher scores with the drug, 3 had equal improvement with drug and control, and 3 improved more with the inert substance than with the drug There were also four scores of +3 and two of +2 with the inert substance

Do these figures really justify his conclusion that the drug is of considerable value?

St Mary Cray, Kent
E Tuckman

VASODILATOR DRUGS IN OCCLUSIVE VASCULAR DISEASE OF THE LEGS

Sir,—The conclusions arrived at by Mr Gillespie [1] cannot be allowed to go unchallenged

Mr Gillespie measured the blood-flow in the foot and calf of patients with and without obliterative arterial disease after intravenous injections of four so-called vasodilator drugs He concluded that, as the vasodilators he used did not increase the calf-muscle blood-flow and often decreased it, all prescribing of vasodilators for the treatment of intermittent claudication is useless The vasodilator drugs he used were tolazoline (' Priscol '), phenoxybenzamine (' Dibenyline '), chlorpromazine (' Largactil '), and promazine

I have found that tolazoline is the least active peripheral dilator used in my series, and I have abandoned the use of phenoxybenzamine in the treatment of obliterative arterial disease. Chlorpromazine and promazine are not claimed by the makers to have any benefit in the treatment of this disease By contrast, I have repeatedly shown [2] that spasmocyclone (' Cyclospasmol '), nicotinyl alcohol tartrate (' Ronicol '), and azapetine (' Ilidar '), used alone or in combination, are the drugs of choice in the treatment of peripheral vascular disease It is ridiculous to condemn the action of satisfactory drugs on the basis of tests carried out with ineffective ones In practice vasodilators are used either by mouth or by intra-arterial injection, and not intravenously If Mr Gillespie wished to disprove the action of vasodilators in the treatment of peripheral vascular disease, he should have used them in this way

The symptoms of occlusive arterial disease develop rapidly after the disease has been present for some years A minor decrease in the blood-flow must finally precipitate the first symptoms The effective vasodilators increase the blood-flow sufficiently to ameliorate these symptoms The method used by Mr Gillespie to measure the blood-flow is not sufficiently accurate to detect small increases in the blood-flow

The long-term effect of drugs in the body cannot be assessed accurately by any method other than clinical trial The vast number of publications describing the advantageous clinical action of the various vasodilators is evidence of their value in the treatment of peripheral arterial disease

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Birmingham 18
R O Gillhespy

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[7] Trimble, A P *Proc R Soc Med* 1957, 50 125
[8] Schlipkoter H W Beckers M *Z ImmunForsch* 1951, 108, 301
[9] Semple, S J G *Lancet* 1959 ii 289
[10] Broom J C *Brit med J* 1951 ii 689
[11] Ross Russell, R W R *Lancet*, 1958, ii, 1143
[12] Mackay-Dick, J , Robinson, J F *J R Army med Cps*, 1957, 103, 186

[1] Gillespie, J A *Lancet*, 1959 ii, 995
[2] Gillhespy R O *Angiology* 1956, 7, 27, *Brit med J* 1957, i, 207, *ibid* 1957, ii, 1543, *Brit J clin Pract* 1959, 13, 608, *Lancet*, 1959, i, 1096

HERPETIC WHITLOW

SIR,—We read with great interest the article in your issue of Nov 21 by Dr Stern and his colleagues on herpetic whitlow amongst the nursing staff in a neurosurgical unit We encountered somewhat similar cases of herpes simplex in the nursing staff a few years ago at a London hospital,[1] but, in addition to cases of whitlow and paronychia as described in this article, there were a few cases of an impetiginous type of infection At first the lesions were like a bullous impetigo, although rarely we noted a small herpetic vesicle in the early stages After that the lesions were more granulomatous like orf and ran a more indolent course than the pyogenic counterpart We also found a distinct difference between primary and recurrent or, more probably, reinfections

Primary infections, confirmed by virological and serological tests, invariably developed multiple lesions, but, unlike the cases described by Dr Stern and his colleagues, we found a constitutional disturbance, fever, and regional adenitis to be common In one of us who developed a primary infection as a result of collecting material for diagnosis from a case of herpetic gingivostomatitis a series of small vesicles appeared four days later around a minute skin abrasion, and after a period of about a week developed into a multilocular vesicle which subsequently took on the appearance of a granuloma Pyrexia (100-101°) lasted for several days and regional adenitis was marked In two cases of recurrent or reinfection in members of the staff with herpes-neutralising antibody at the time of onset, lesions were strictly localised to a single vesicle on the thumb or digit with a small area of surrounding erythema It was also noted that this type of lesion healed very much more rapidly than the primary

In all instances a clear history of contact existed, there being cases in the ward of generalised herpes simplex or eczema herpeticum A senior nurse who developed a solitary lesion on the finger was also subject to recurrent labial herpes, but in this instance it appeared that it was not an autogenous infection but she had become reinfected from one of the cases of eczema herpeticum In this latter disease the virulence of herpes virus seems to be enhanced by the patient's eczematous diathesis, and the infection is often alarming, sometimes fatal, and compared with other forms of herpes in a non-eczematous patient the risk of contagion is greater

We also found the examination of smears taken from the base of the vesicles to be of value in diagnosis The typical appearance of multinucleate epithelial cells, which are seen only in herpes simplex or varicella-zoster infections, enabled a diagnosis to be made within a few minutes, which could then be confirmed by further laboratory investigations

London

R T BRAIN
J A DUDGEON

HYPOPARATHYROIDISM WITH STEATORRHŒA

SIR,—In view of the occasional interest shown in the combination of hypoparathyroidism with steatorrhœa (e g, by Williams and Wood [2]), particularly since we drew attention to it in *The Lancet*,[3] it is only right that I should report the conclusion to the story of our first patient [4]

Shortly after our report [3] appeared she returned to hospital with masses in the abdomen, which were found at laparatomy to be lymphomatous This malignant growth had virtually replaced the whole pancreas and infiltrated the wall of the small bowel throughout its entire length She died shortly afterwards outside hospital and no necropsy was performed

The fact that the diagnosis of her malady was not idiopathic steatorrhœa, as we had suspected, makes no difference to the interest in its connection with hypoparathyroidism—the combination apparently including the symptom, "steatorrhœa", rather than any particular basic disease

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Groote Schuur Hospital,
Observatory, South Africa

W P U JACKSON

CRANBERRIES AND THANKSGIVING

SIR,—In the issue of *The Lancet* of Nov 28, 1959, in the column devoted to Public Health (appearing two days after our American Thanksgiving had been observed in a literal welter of cranberry sauce), a comment on both cranberries and Thanksgiving is to be found

In regard to the warning issued by the Secretary of Health, Education and Welfare pertaining to contaminated cranberries, it is pertinent to observe that Mr Flemming, in calling attention to the situation, was doing only what the law requires, and Americans, as is well known, are a law-abiding people The fact that a person would need to eat 15,000 lb of contaminated cranberries daily for a long period to suffer any ill effect is a poor argument, many persons on this side of the Atlantic would gladly do so in order to defend a principle

In the very first paragraph, in reference to the background of Thanksgiving, the suggestion is made that many of the Pilgrims failed to survive their first American winter and that those who did survive accomplished this feat because of a bountiful harvest The sad fact is that the Pilgrims set foot on Plymouth Rock on Dec 21, 1620, too late to harvest a crop that had not been planted, and that those who survived did so because of a mild winter, the friendliness of the still unconditioned Indians, and the British guts that they brought with them

JOSEPH GARLAND
Boston, Mass
Editor, *The New England Journal of Medicine*

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—Mr Azie [1] has done well to direct attention to a method of resuscitating patients who are gravely ill from massive intraperitoneal hæmorrhage, and for whom blood-donor or blood-bank facilities are not available This is the simple but strangely neglected procedure of injecting the patient's own blood back into the veins after straining off all obvious blood-clot Autotransfusion, as it has been called, is particularly useful in the graver cases of ruptured tubal pregnancy

The method is, however, by no means new Dr Logan,[2] working in a South African mission hospital, has recorded 40 cases of autotransfusion with recovery in every case Dr Markowski, working in Belize, British Honduras, has given me details of 100 cases of ectopic pregnancies so treated with survival in all but 1 case So useful has he found this method that he has sterile apparatus, including a mechanical sucker, constantly available in his operating-room The subject is discussed in Munro Kerr's *Operative Obstetrics* (6th ed, p 761)

During the past 25 years I have used autotransfusion on many occasions It is easy and can be used without the time-consuming matching and cross-matching of bloods Working in a teaching hospital, I feel it a duty to demonstrate the method from time to time in order to impress upon students that this is a possible way of saving a patient's life when blood-banks and blood-donors are not available

Mr Azie does not appear to use any anticoagulant when collecting the blood Were he to do so he would find that the

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1 Brain, R T *Brit med J* 1956 i, 1061
2 Williams, E, Wood, C *Arch Dis Child* 1959, 34, 302
3 *Lancet*, 1957, i, 1079, 1086
4 Jackson, W P U, Hoffenberg, R, Linder, G C, Irwin, L *J clin Endocrin* 1956, 16, 1043

1 Azie, A A *Lancet* 1959, ii, 1093
2 *S Afr med J* 1948, 22, 793

method is even easier and more reliable. My practice has been to cup the blood out of the abdominal cavity by means of a small gallipot, to strain it through several layers of gauze in a glass funnel, and to collect the fluid portion in a sterile flask containing 2 g. disodium citrate and 3 g. dextrose in 120 ml. water (the normal "bleeding" flask kept for blood-donors). As soon as the first bottle is ready it is connected to the intravenous-saline drip apparatus which has been set up before starting the operation.

Naturally, only recently shed blood is suitable, but it is in the most urgent case of all—the ruptured ectopic pregnancy with massive intraperitoneal bleeding—that such blood is abundantly available. The method is less applicable, but is also less necessary, when intra-abdominal bleeding has already been present for several days.

It is strange that this simple procedure, which can be lifesaving in so many instances, is not better known. Perhaps the present-day availability of donor blood has made our younger surgeons contemptuous of the older and simpler methods of transfusion.

The Nuffield Department of
Obstetrics and Gynæcology,
The Radcliffe Infirmary,
Oxford.

J. CHASSAR MOIR.

PRECORDIAL CATCH

SIR,—Allow me to add to the letters on the precordial catch—letters which may illustrate Dr. Asher's thesis that naming a condition brings it into clinical existence. I have no evidence to submit, but I should just like to record the naïve assumption that this pain is caused by some "catch" (a transient wrinkling, friction, or folding) of the pleural membranes.

Amsterdam.

P. J. THUNG.

URINARY INFECTION IN THE NEWBORN

SIR,—I was very interested in the paper by Dr. James (Dec. 5). I have been about to start a similar study and among other things had hoped to see if there was any correlation between cell-counts on uncentrifuged urine and the approximate cell-count per high-power microscopic field on centrifuged urinary deposit as used in most laboratories. Did Dr. James make any observations on these lines?

There has been an unusually high incidence of urinary infections in newborn infants in recent months hereabouts, fortunately none fatal. In one infant considerable jaundice and anæmia occurred, which appeared to be hæmolytic in origin, and as we were unable to find evidence of blood-group incompatibility or other cause for the hæmolysis, we attributed this to the renal infection, the hæmoglobin and bilirubin on admission on the 10th day of life were 11·3 g. and 10 mg. per 100 ml., the latter rising to 15 mg. on the 11th day, and the former falling to 6·3 g. on the 29th day. Another infant had moderate jaundice and anæmia, again presumed due to the renal infection. It would be interesting to know if any of Dr. James' cases showed hæmolytic anæmia.

With regard to the mode of invasion of the urinary tract, it was suggested by Delaney[1] that in addition to the hæmatogenous route, infection may spread along the lymphatics to the kidneys, or ureters, from an infected umbilicus. The first infant mentioned above had a severe omphalitis, and the organism cultured both from umbilicus and urine was of the coliform group. It is remarkable that the three infants reported by Delaney with omphalitis and pyelonephritis each developed kernicterus, apparently unassociated with blood-group incompatibility.

Few will disagree with Dr. James that treatment of urinary infections should be continued for not less than six weeks, with regular follow-up for a year or longer. I presume from her use of a fairly large dosage of sulphonamide for the first two weeks that Dr. James believes the main lesion in most cases of urinary infection to be pyelonephritis, an adequate serum level of the drug being required to combat the interstitial renal infection; such is certainly my view.

BRIAN MCNICHOLL.

INFLUENZAL ENCEPHALITIS

SIR,—In his letter of Dec. 19 Dr. McGill may be ascribing to corticosteroid therapy ("modern antiallergic therapy") what is in fact the natural course of the disease. In the 2 cases I reported during the epidemic[1] the most striking clinical features were the severity of the illness and the unexpected rapid recovery. We did not use cortisone but only antibiotic cover. Our first case was in extremis for 3 days and the prognosis seemed quite hopeless. A very similar course was shown by case 2 of Dunbar et al.[2]

Of the 4 cases reported by McConkey and Daws[3] only 1 was treated with cortisone, and, although they noted "some clinical improvement" 4 hours after commencing therapy, she apparently remained in coma for a further 5 days and then "recovered consciousness rapidly". It is hard to believe that the cortisone played a major role in the course of her disease.

Queen Mary's Hospital
for Children,
Carshalton, Surrey.

V. DUBOWITZ.

INSULIN REACTION AND DIABETIC RETINOPATHY

SIR,—It is accepted that well-controlled diabetic patients have less vascular complications than those under poor control. Patients are sometimes observed, however, whose vascular complications become progressively worse in spite of the ideal control of their illness with diet restriction and insulin. On the other hand, patients are seen who have had free diet and no insulin with no vascular complications.

We observed a 60-year-old man whose diabetic retinopathy appeared after insulin reactions,[4] and another whose retinal hæmorrhage occurred during a urine-sugar-free period on insulin treatment. The experiment of Dünner et al.,[5] which demonstrated that insulin produced retinal hæmorrhage in dogs, supports the possibility of the occurrence of such undesirable changes in the retina as observed by us. Fortunately, I found the recent article of Jahnke[6] about the unpleasant effect of insulin on the retina. He quoted several cases from the literature in which insulin seemed to provoke retinal changes. He pointed out that diabetic retinopathy has been increasing with the spread of insulin treatment, and that this increase is not merely due to the prolongation of survival of diabetic patients by the progress in treatment.

We speculate that the unfavourable effect of insulin may be due to an increased release of adrenocortical hormone, resulting from a fall in blood-sugar. Administration of cortical hormone or corticotrophin sometimes provokes microaneurysms and other changes in the retina. The recent studies of Saito et al.[7] again confirmed an increase in urinary corticosteroid excretion in diabetics with vascular complications, compared with those without complications. Basing his views on the experiments of Müller and Petersen,[8] Jahnke proposed increased permeability

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[1] Delaney, W. E. *J. Pediat.* 1959, 54, 36.

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[1] Dubowitz, V. *Lancet*, 1958, i, 140.
[2] Dunbar, J. M., Jamieson, W. M., Langlands, J. H. M., Smith, G. H. *Brit. med. J.* 1958, i, 913.
[3] McConkey, B., Daws, R. A. *Lancet*, 1958, ii, 15.
[4] Goto, Y., Fujino, K. *Endocrinol. japonica*, 1959, 6, 9.
[5] Dunner, L., Ostertag, B., Thannhauser, S. *Klin. Wschr.* 1933, p. 1054.
[6] Jahnke, W. *Hippokrates*, 1959, 30, 279.
[7] Saito, T., Yagi, T., Sasaki, H., Otsuka, H., Hoshi, A., Uemura, J. *Tohoku J. exp. Med.* 1959, 70, 247.
[8] Müller, E. F., Petersen, W. F. *Klin. Wschr.* 1926, p. 1025.

of the blood-vessel wall I feel that the strictly controlled state, where hypoglycæmia may occur, is harmful to diabetic patients, especially to those with retinopathy

Philadelphia YOSHIO GOTO

OBESITY

SIR,—Professor Yudkin's article of Dec 19 throws much light on the confused subject of obesity Further clarification of the use of the term "overweight" and of the effect of excessive food intake seems desirable

Overweight is determined by comparison of weight with accepted standards for age, height, and sex It is a statistical concept, objectively determined by physical measurement and it is not constantly correlated with obesity Obesity is basically an æsthetic, or at least clinical, concept, subjectively determined and produced by the distortion of body contour by fat

I found in a series of 200 adult male patients seen consecutively in general practice that 3 muscular men were 40% over standard weight for age and height they were certainly not obese Similarly those with poor muscular development can be little overweight, or even of standard weight, and yet be obese Clinical judgment, not comparison of weight alone, establishes the presence of obesity

Common experience challenges the statement that "it is simply not true that most people—or any single person—can eat more food or less food without changing weight" Dodds,[1] in a discussion on obesity at the Royal Society of Medicine, referred to an experiment in which subjects whose weight had been constant for many years were kept in bed and given two or three times their normal diet. They did not increase in weight although controls put on weight easily Such an observation seems very credible and it would be interesting to know whether it has been confirmed There is nothing inherently improbable in the idea that certain people—even most people—are able to respond to excessive food intake by increased metabolism I have not found in Professor Yudkin's article the evidence that this is not so

London, W 2 JOHN MCMULLAN

DIMINISHED RESPONSIBILITY

SIR,—Dr Maddison (Aug 15) advocates the doctrine of determinism The "argument in brief", on its behalf, is that "the path which we take is unswervingly determined by our personality structure" In other words, we are determined, because we are determined This "argument" contrasts unfavourably with the three proofs for free will

Firstly, intellective consciousness apprehends immediately and experimentally, in the concrete, not only the act of will, but also its freedom While we are deliberating or taking counsel, and while we are terminating our deliberations or consultations, we are quite conscious that the selected end is imposed on us by our own will, and that we are not irresistibly or necessarily drawn to it Our intellective consciousness clearly distinguishes the action to which we are determined, from our free acts When someone says "tree", I am necessitated to exercise an act of apprehension of "tree", and I have no consciousness of freedom But when I go for a walk, or draw a line, I am conscious of acting from free choice, and that I can freely stop at any point This immediate experimental evidence cannot be met by simply denying freedom Nor can it be explained as mere ignorance of cosmic forces and laws

Secondly, there are facts which cannot be explained unless freedom of choice be admitted These include the making of plans, promises, and appointments, legislation, self-approbation, self-reproach, and remorse, the giving of commands and prohibitions, advice, rewards and punishment, praise and blame We can act against our physical inclinations, as when we refuse a chocolate lest we overeat, or when we get out of bed early on a cold morning to go to Church Surely the latter is not accounted for by a church-organist among my human ancestors, nor by a bat-in-a-belfry among my pre-human ancestors (if any)

The third and greatest proof of freedom, from the objective infinity of the human intellect, is too long for exposition here

Because there are things in man which are chemical and material, therefore everything in man is chemical and material, and because man is pre-moved, therefore he is also predetermined, is neither good logic nor good science "As if we were villains of necessity, Knaves, thieves and liars by spherical predominance, drunkards, liars and thieves by an enforced obedience of planetary influence!" Winston Churchill gave even shorter shrift to the spiritless deterministic psychiatrists, in vol IV of *The Second World War* The opinion of the regimental sergeant-major, about the recruit "determined" to keep out of step, was unprintable—but justified

Dr Madison says that "the existence of 'good' and 'bad'" are "products of the human mind" So the apple which I threw out was not really bad, but I was bad-minded And "the facts of morality" are merely "products of the human mind" Which means that respecting my neighbour's property is not good in itself, nor is thieving bad in itself But only as my mind, or the mind of a dictator, makes them!

However, there is hope for Dr Maddison yet He introduces "accountability", which is not accountable except from free will And he contradicts his own doctrine by informing us that "civilised man naturally assumes responsibility for the effects of his action on others"

Sydney V J KINSELLA

POSTCOITAL EXAMINATION OF SEMEN

SIR,—I was deeply perturbed by Mr Dunn's letter in your issue of Nov 28 The investigation and treatment of subfertility, especially in the male, have made considerable advances in the past ten years, and if we accept Mr Dunn's arguments and methods we shall deprive our patients of the help they can expect from us

First of all, I should like to challenge the assumption that subfertile men cannot be improved Since the time when we began to realise the importance of testicular temperature regulation, and the effects of its disturbances upon spermatogenesis, it has become a commonplace to see subfertile men recover A letter such as this is not the place for extensive explanations and references, but I shall be glad to supply the latter to anyone interested For the present I will only say that I have not met anyone with *personal* experience of these methods who maintains Mr Dunn's and his authorities' traditional pessimistic outlook

If it is true that subfertile men may be improved, then obviously a precise and consistent method of semen examination is essential in assessing the patient's original state and progress This, of course, requires seminal specimens produced by masturbation or coitus interruptus, and there is no adequate alternative The method of "postcoital urethral drainage" may not have been described in the literature, but I have met with patients investigated in this way repeatedly One such case was sent to me with an inquiry whether his apparent sterility was beyond repair, a proper semen test showed him a highly fertile man, and his wife conceived promptly after correcting a minor fault on her side Another man investigated in this way had prolonged courses of hormones and vitamins intended to cure his "oligozoospermia" Finally he was given a hopeless prognosis, but a proper semen test also showed perfectly normal findings The postejaculatory urethral residue is in no way representative of a man's fertility and any verdict based upon it must be regarded as guesswork.

The postcoital test has been in constant use for many years, and I think one may regard it as a sine-qua-non in the investigation of an infertile couple After all, the first requirement for fertilisation is a dense and active sperm population in the cervix, and without this further gynæcological investigation may be a waste of time But despite its very great value, this test has its limitations Unless we are quite clear as to what it can and cannot tell us even a perfectly conducted postcoital examination may mislead us disastrously Mr Dunn's statement that failure to find spermatozoa in two postcoital tests suggests an azoospermic husband is truly alarming! I see amongst my patients quite regularly couples who produce persistently "blank" postcoital results, despite good semen, œstrogenic mucus, and apparently perfect sex function these are cases of a purely "mechanical" failure of insemination, and there are quite a number of reasons why this may happen. Some uterine displacements may turn the cervix into one of the fornices, shielding it from the ejaculate, the couple may use a coital position making for poor penetration, a parous vagina may be so lax that the ejaculation takes place into a pocket of loose mucosa and sperms never reach the cervix, the man may have a hypospadias, and so on A complete list would overburden this letter, but anyone familiar with the postcoital test will be aware of the problem. Incidentally, the correction of these faults usually proves very simple, once the diagnosis is established.

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[1] Dodds E C *Proc R Soc Med* 1950, 43, 343

I must also raise some criticism of technical details of the postcoital test as described by Mr Dunn

Firstly, to remove only a drop of cervical mucus with artery forceps may produce very misleading findings I usually aspirate the whole contents of the cervical canal, and time and again I find some portions of the mucus poorly invaded, or even "blank", when other portions may be teeming with active spermatozoa Therefore poor findings in only one drop of the mucus may be of no significance

Secondly, for the same reason, it is patently impossible to estimate the husband's sperm density from even a complete aspirate of the postcoital mucus since we should not know which of the variedly populated fractions is representative

Thirdly, it is useless to attempt an estimate of the husband's sperm morphology from even a stained postcoital preparation. Only the best spermatozoa invade the mucus since most of the abnormal forms are either immotile or sluggish In the past, when I used to stain my postcoital specimens as a routine I frequently found in them no more than 3–4% of abnormal spermatozoa, even when the direct semen test might show up to 40–50% of morphological abnormalities I believe this is generally recognised by workers who use this method

Lastly, it is surprising to see the statement that in the postcoital test "occasionally motile spermatozoa are seen after sixteen hours" Many of us have seen excellent postcoital results 2–3 days after intercourse, and a few live spermatozoa even after 6 days Most of my own routine tests are done 10–16 hours after coitus, and personally I am inclined to regard a postcoital test after less than 2 hours as of doubtful value For what we want to learn from this test is whether good numbers of healthy spermatozoa survive in the cervix after being exposed to the hazards they must encounter And after 2 hours or less many spermatozoa may still be alive which will never reach the cervical canal, or survive in it if they do

One might scrutinise the reasons for introducing these indirect and roundabout methods instead of the well-tried direct semen test Mr Dunn mentions moral standards and overlooked sensibilities The former, I should say, would apply only to certain religious denominations To many men the act of masturbation or coitus interruptus, in a most worthy cause, is not more a moral issue than the gynæcologist's examination is to their wives As to sensibilities, one might ask whether a man who feels deeply would expose his wife to embarrassing and sometimes painful investigations before eliminating the approximately 40% chance that he himself carries the main infertility factor Among my own series of over 12,000 husbands the incidence of complete azoospermia is little short of 10%, and that of grossly impaired semen very much higher It is obvious therefore that failure to assess the male factor accurately would condemn many women to a great deal of unnecessary investigation, discomfort, and eventual frustration My personal impression is that usually a man's reluctance is based upon fear of being found at fault. This, I think, applies equally to women, yet we do not hesitate to examine them And just as we can reassure a frightened woman by explaining the need for precise diagnosis, a man will be capable of overcoming his misgivings if we appeal to his reason and his sense of fairness

London, W 1 H A DAVIDSON

CHRISTMAS FACTOR IN THROMBOTEST

SIR,—There appears to be some misdirection of emphasis in Dr Nour-Eldin's letters (Nov 21 and Dec 12) on the thrombotest devised by Professor Owren [1] This new method is not designed to detect Christmas disease but to control anticoagulant therapy during which Christmas factor in addition to prothrombin and factor VII are depressed Even if the method is shown to be only a little more sensitive than existing *practical* ones the contribution of Professor Owren cannot be ignored

We have been fortunate in having had several months' experience with thrombotest The essential reagent is sent out in lyophilised form easily reconstituted in a few minutes and the test is very simple to perform Our final assessment is nearly ready for publication.

In two cases of Christmas disease tested by us with thrombotest the clotting-times were about 10 seconds longer than normal Professor Owren, in a personal communication, has pointed out that when the test is carried out with plasma from a case of Christmas disease (concentration of Christmas factor below 1% of normal and all the other factors at 100% of normal) and then with plasma from a normal subject (concentration of all the factors at 100% of normal) the difference in clotting-times was only 6–8 seconds However, when the extrinsic clotting system is depressed during anticoagulant therapy the sensitivity to depressions in Christmas factor increases, using dilute thromboplastin reagents [2]

The thrombotest reagent appears worthy of careful clinical trial and may well prove to have a place in the routine control of anticoagulant therapy It is apparently being used extensively in Scandinavia

Anticoagulant Therapy Service,
Department of Clinical Pathology,
Manchester Royal Infirmary

H LEMPERT
L POLLER.

A CENTRAL LABORATORY FOR OCCASIONAL INVESTIGATIONS

SIR,—A number of investigations essential to the diagnosis or management of disease are demanded so rarely or are technically so inconvenient that they are not everywhere readily available They are often done as a courtesy by interested research-workers, who naturally may not undertake them always or promptly

Now that the Public Health Laboratory Service is being remoulded, the National Health Service might well establish a central laboratory able to estimate routinely follicle-stimulating hormone, urinary catecholamines, protein-bound iodine, and transaminase, to name only a few of the tests occasionally required by the general physician It would play a role in biochemical and endocrinological diagnosis as important as that of the bacteriological reference laboratories in their sphere

Oxford T H HUGHES-DAVIES

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[1] Owren P A *Lancet* 1959 ii 754
[2] Waaler, B A *Scand J clin lab Invest* 1957, 9, 322

Obituary

HUGH DONOVAN

M B Birm , F R C S , F.R.C S E

Mr Hugh Donovan, senior urologist to the United Birmingham Hospitals, died on Dec 6

Born in 1897, the son of Lieut -Colonel R T Donovan, R A M C , he was one of a family of doctors well known in the Midlands He was educated in Birmingham at King Edward's School and the university During the 1914-18 war he served in destroyers as a surgeon-probationer, and he did not qualify until 1919 He was one of Prof Seymour Barling's notable band of house-surgeons, but he did not immediately turn to surgery, for he joined the Indian Medical Service for a brief spell But once he had chosen surgery as his specialty his chief interest was always urology, and he studied this subject in London, where he was for a time a clinical assistant at St Peter's Hospital, before he was appointed assistant surgeon to the Queen's Hospital in Birmingham He remained a general surgeon with this special interest until shortly after the late war, when the death of his senior colleague, B J Ward, left him with more and more urological work Finally Donovan gave up general surgery entirely This change enabled him during the last decade to lay the foundation of a urological department, and his success was lately recognised by an invitation to become president of the British Association of Urological Surgeons in 1960, an invitation which he had to refuse because of ill health

B N B writes

" It is my misfortune to have known Hugh Donovan only during the last twelve years, for throughout these years he appeared a lonely man seeking solace in work after the early death of his wife, to whom he had been devoted But this is not to say that he was unapproachable, indeed to be *à deux* with him was to be sure of amusement and gentle understanding Despite occasional moments of contention, moments which revealed the degree of his usual self-control, gentleness pervaded his surgical life and his everyday affairs—gentleness mixed with charm and whimsy, both reminders that his Irish ancestry was stronger than his Midland upbringing Courage he had in full measure, he did not hesitate to transect the vena cava in order to transpose a ureter where lesser men would have quailed, done the reverse, and risked a ureteral stricture later He was industriousness personified, even to a fault, since it never occurred to him that his own unceasing labours necessarily involved others and might bring them to exhaustion, not that his junior staff ever complained, since his approach to any subject, conventional or otherwise, was from such an unusual slant that it would be certain to stimulate or amuse—often both Over and above there was the transparent honesty and integrity of a man tested beyond personal ambition "

DOROTHEA CLARA NASMYTH

M A. Dubl , M D Lond

Dr Dorothy Nasmyth, who died on Dec 12, was something of a pioneer She was the first woman to read physiology at Oxford (and one of the few who have ever taken a first in this subject) and she was the first woman general practitioner in Oxford She qualified in 1906 and during the 1914–18 war worked in Serbia during the typhus epidemic

A M writes

" Dorothy Nasmyth's small stature, quiet voice, and slow speech hid an outstanding intellect, almost uncanny powers of perception and judgment, and a great devotion to medicine and to people But she was not ambitious She rejected the chance of an academic career because she loved general practice Her clinical judgment was remarkable and to the end of her life she often made diagnoses which seemed to be both unlikely and extraordinary, but which time or investigation proved to be correct. She read widely in many branches of medicine and always made a point of learning what she could from any specialists, younger doctors, or medical students who came her way Her humble approach often gave them the impression that she was old and out of date, but her immediate understanding and her perspicacious comments soon revealed her wide knowledge of even the most modern developments Until her final illness she continued to attend lectures and clinical meetings, often driving many miles to do so

" She had many interests outside her work Perhaps the chief of these, apart from devotion to her husband and family, was a love of animals I first met her when I was ten, through the riding-school that she ran with her son and daughter The friendship, despite an age difference of some forty-five years, continued to develop until her death, for she had the ability to cross the barrier between generations She could talk as one individual to another with people of any age She seemed to retain in maturity and age the essence of childhood and youth that most people lose in passing "

DAVID ARTHUR KETCHEN CASSELLS

M D St. And , M R C P E

Dr D A K Cassells, formerly chief medical officer to the alkali division of Imperial Chemical Industries, died on Dec 16 at Northwich

He was born in Fife in 1896, the son of a Scottish dominie. After serving in the 1914–18 war as a combatant, he qualified from St Andrews University in 1923 He held house-appointments at Dundee Royal Infirmary and then went into general practice in Herefordshire In 1938 he took the M D at St Andrews with honours and left his practice for further study at the Postgraduate Medical School of London, taking the M R C P E in 1939

In 1940 he became medical officer to a factory where for the first time in this country tetraethyl lead was manufactured The process was full of little-known hazards, but because of his continuous vigilance there was no case of intoxication in the factory Cases, however, did occur elsewhere from time to time, and he was often called in to advise In 1946 with Sir Charles Dodds he published a classic account of tetraethyl-lead intoxication, including 25 case-histories During the late war he was appointed consulting physician to the Victoria Infirmary, Northwich, where he helped to set up a small panel of blood-donors which, until blood-banks came into being, was of great use After the war he became the first full-time chief medical officer of the alkali division of I C I He retired in 1958 Outside his work he found relaxation in bridge and fishing He leaves a widow

Diary of the Week

JAN 3 TO 9

Tuesday, 5th

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr Joseph Minton Ocular Manifestations in Clinical Neurology
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Prof David Whitteridge The Calcarine Cortex and Cerebral Organisation.

Wednesday, 6th

ROYAL FREE HOSPITAL, Gray s Inn Road, W C 1
5 P M Dr Ellis Dresner (Harvard) Latex Fixation Reaction

Thursday, 7th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P M *Neurology* Dr J B Cook, Mr Thomas Moore, Mr D Innes Williams The Paralysed Bladder

Friday, 8th

ROYAL SOCIETY OF MEDICINE
5 30 P M *Anæsthetics* Dr A R Hunter, Dr J M Inglis Value of Controlled Respiration in Neurosurgery
INSTITUTE OF LARYNGOLOGY AND OTOLOGY 330, Gray s Inn Road, W C.1
3 30 P M Mr C Gill-Carey Otitis Media

Notes and News

THE PREP SCHOOL

PREPARATORY schools are facing a difficult future, for in the next few years, as State schools and independent schools move closer together, more and more boys are likely to enter or leave preparatory schools at the age of 11 A short report [1] on them which has lately appeared is of exceptional interest, because it reconsiders the aims of teaching without much regard to the requirements of the public schools At present the universities call the tune to the public schools, which in turn impose a pattern upon the preparatory schools With greater mobility within the educational system this stranglehold will relax, and even now there are, it seems, more boys in preparatory schools than the public schools can accommodate.

The report is unusually imaginative It argues that Latin should be taught only to those likely to be academically capable of benefiting from it, and it recommends a later start in this subject The section devoted to the early teaching of science is especially good. Regarding such teaching as a means of "stimulating interest in natural things and of supplementing a boy's inherent interest in how things work", it goes on to outline a syllabus actually in use which appears to be unexceptionable The need for a drive for greater literacy and fuller attention to cultural interests is emphasised There is an admirable section on the opportunities inherent in the conception of physical education

Parents and those interested in the generation now growing up will find this report stimulating It is hard to avoid a sense of frustration when one realises how much could be done if there were only the money No reference is made to the lamentable shortage of good teachers in preparatory schools today The position is getting worse as the older ones go Unless and until the conditions and pay attract the right men, there is small hope of these brave recommendations being fulfilled

CLEANSING AND STERILISATION OF HOSPITAL BLANKETS

EFFORTS are being made in many hospitals to improve the hygiene of bedding and to provide each patient with freshly laundered and disinfected blankets This is certainly desirable on æsthetic grounds, and there are apparent though unproven bacteriological advantages But hospital authorities wishing to consider these matters must search widely for the available facts and opinions The King Edward's Hospital Fund for London has now done this for them, and its interim report [2] contains extracts from many published papers and from replies to a questionary sent out by the Fund's division of hospital facilities The subjects discussed include the role of unsterilised blankets in hospital cross-infection, the problems of washing and sterilising them, and the different types of blanket that are now to be had, their cost, and their acceptability to patients and nurses On very few of these problems can a clear answer yet be given, and it is perhaps a pity that this interesting summary has been published before some of the current large-scale investigations are complete. Nevertheless, it brings together a set of references which will be useful to those who are planning trials of their own

HOSPITALS YEAR BOOK

THE new edition of this useful and handy annual [3] has appeared punctually and will be at hand during 1960 to offer reliable information Besides the hospital directory there are sections giving particulars of blood-transfusion services, Government departments, statutory bodies and organisations, local health authorities, executive councils, Whitley councils, and hospital contributory and provident schemes A substantial reference section includes indexes to statutory instruments and official circulars, legal notes, and summaries of reports, and a short bibliography of recent publications about hospital topics ranges from "accounting and finance" to "staffing" Mr J F Milne, the editor, in his survey of the past year soberly discusses the problems which dog all progress He welcomes the new Mental Health Act but warns that its effect may be hindered by lack of money and staff He welcomes work study as a necessary tool for a modern service, but points to the danger that "time and effort devoted to work study will not be matched by commensurate time and effort in applying its results"

University of Cambridge

On Dec 12 the degree of M CHIR was conferred on P P Philip (by proxy)

University of Durham

On Dec. 19 the degrees of M B , B S were conferred on the following

Bandele Akinola Abovade, Lilian F C Beattie, Kenneth Beveridge, Kenneth Bolam, T M Bolam, Moira M A Browne, W K. Deegan, J D Etherington, J G Goundry, P J K Maskery, G W Odling-Smee, Christine M Peacock, F A Rafique, Susan J Richardson, Mashood Babatunde Odemuyiwa (in absentia)

University of Leeds

At recent examinations the following were successful

M D—John Gibson, T K Marshall, Ronald Spink

M.B , Ch.B—Helen M Hoyle, J M S Pearce, J H Wetherill (second-class honours), Jill E Awcock, J A C Bailey, Walter Barnes, Ann G Benson, R E Blagg, A G Bond, Ian Cliffe, J A Dacre, Irene M Dunderdale, Shirley M Ewart, T R Forrest, Kenneth Fox, J M France, Margaret Hallas, Dharmchand Heeralall, Jennifer A Homeshaw, R V Howarth, Derek Hoyle, Florence S Hutchinson, Hamid Ikram, K J Kedwards, G P Kirkland, D H Mellor, Kenneth Oldroyd, B A Pell, Raymond Plowman, Elizabeth Rowe, Eddys E Sherwood-Cundall, Kenneth Thornber, R A N Welham, Elizabeth A Wilford.

University of Liverpool

On Dec 18 the following degrees and diplomas were conferred

M.D—Constance M Davis, D A P Evans, J E Riding, J G Warbrick

Ch M—*Ranjit Basu, *Roger Brearley, John Humphreys, *P K. Tamaskar

M Ch Orth—A C Da Roza (gold medal), J A Adams, K V Chaubal, A W B Heywood, D C MacPhail, B T O Connor, M Y Rai, M L Rajakaruna, *B F Regan, L N Vora

M.B , Ch.B—Geoffrey Balderstone, K R Ball, T D Birtles, J A Q Blukoo-Allotey, Judith M Burgess, Kenneth Cartwright, Essilt Evans, R G V Hughes, B H E James, J H Lloyd, G W McKenna, C J Merry, Patricia A Moore, Ronald Pactor

D.M R.D—P Daranond, H F Davies, C D Krasner

D M.R T—Varunee Amatyakul

D T M & H—D R Bell, G N Bhadresa, S M Bieber, R M Briggs, J R. Cope, A A Darkwa, D S Gilchrist, D R W Haddock, R Harris, R B Hawes, M M Husainee, T D Jeyachandran, W L Johnson, E D Mahajan, G D E Morris M. A Newland, W I B Onuigbo, C R Rao, V R Rao K B H Reddy, J H Rouch, J T Sorley, L F Tinckler, L Tsere, Sutee Ujjin, J T Weir, D G Young

* In absentia

University of Manchester

At recent examinations the following were successful

M B , Ch.B—G A Cumming Shirley Currie, T C Davies, P L S Dixon, D L Easty, Valerie K Frazer, F A Hindley, F R Hirst, C E Horsfall, W R Hutton, M J Imrie, A W Jackson J H Jones, Frank Kemble, N P Mallick, Shirley A Maxwell, Doreen Mullins, Rosemary G Mitchell, K J Noblett, Doris E Probert, Diana H Seddon, Shirley E. Stanworth, J R Thelwell, J B Thomson Margaret Ward, Sylvia A Wood

University of Sheffield

Dr John Knowelden has been appointed to the chair of preventive medicine and public health.

He was educated in London at King s College and St George's Hospital After qualifying in 1942, he served as a surgeon lieutenant in the R.N V R till 1946 After demobilisation, with a Rockefeller fellowship in preventive medicine he spent a year at the Johns Hopkins School of Hygiene and Public Health, Baltimore In 1949 he was appointed to his present post of lecturer in the department of medical statistics and epidemiology at the London School of Hygiene and Tropical Medicine He is a member of the Medical Research Council statistical research unit, and he was secretary of the M R.C poliomyelitis vaccines committee which conducted the 1956 field trial of British poliomyelitis vaccine Dr Knowelden is a joint editor of the *British Journal of Preventive Medicine*

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[1] Foundations report of a committee appointed by the council of the Incorporated Association of Preparatory Schools Ipswich W S Cowell 1959 Pp 47 Copies may be had from R A. Harrison, Snape Hill, near Saxmundham, Suffolk, for 2s (post free)

[2] An Interim Report on the Cleansing and Sterilising of Blankets King Edward s Hospital Fund for London 34, King Street, London E.C.2 Pp 59 2s post free

[3] Hospitals Year Book 1960 London Institute of Hospital Administrators (75, Portland Place, W 1) 1959 Pp 1166 59s 6d

University of Bristol

At recent examinations for M B , CH B the following were successful

R I A A Aubee, J A G Benson, G C Duff, H W Haskins, D R M Heighton, J P A Hill, R C Hodge, G W E Lockett, Madeline D Mayne, D T H Randell, Dorothy M I Sibbald, D J Stayte, Madueke Ugwunze, Ranjit Jayakar Undugodage

University of Edinburgh

On Dec 18 the following degrees and diplomas were conferred

M D—R R Gillies, *C G I Gordon, J C Gould, R S McNeill, H W Simpson (commended for thesis), Morag S Macdonald

Ph D (*in the faculty of medicine*)—A W Williams

M B , Ch B—J W S Angus, J A Birtchnell, J B McG Fleming, J D Gilleghan, Peter Gordon, D J Harrison, J M Henderson, R. G McGown, C J McKeown, J A L Mayhew, R G Moses, J E M Robertson, R T A Ross, W G Russell, Prasert Sukhum, W R Sullivan, R N T Thin, T G S Wilson

D P H—Agnes E Whitter

D M R D—A A H Brown, G M Fraser, A F MacDonald, I R Pyle

D M R T—James Frame, J F Pringle, H G Whiston

* In absentia

Queen's University of Belfast

Dr W E Glover has been appointed supernumerary lecturer in physiology

Royal College of Surgeons of Edinburgh

At a meeting of the college on Dec 18, with Prof John Bruce, the president, in the chair, A H Jacobs, P R F P S G , V C Rambo, F A C S , and J D Wade, F R C S , were admitted fellows without examination

The following were admitted to the fellowship

J B Anchen, B J Bowden, B C Bracken, Manindra Nath Brahma, D Pui-Chee Chan, Raghunath Deshika Char, G D Chisholm, E Poh Hwye Chu, E C Cowan, A C B Dean, Lakshman Chandra Dutta, Anup Mangesh Gokarn, P A Goodwin, C E Graham, E C G Lee, Brijlal-Chananram Gupta, S D Holloway, Mominul Huq, A R Isaac, G R James, Vasant Venkatrao Kayarkar, J A Kennedy, I F Kerr, K G Kling, Izak Labuschagne, W M L Laubscher, H I Leigh, P J Lethlean, J H Lowry, Abdel Wahab Reda Mabrouk, J G Mathie, Brian Measday, Mookkassanmirveettil Pullare Achutha Menon, K K Merten, W G Millar, J C Milliken, Shaikh Mohammad Monif, John Morgan, Jack Norman-Smith, T G O'Donovan, Thotathil Achuthan Paraman, Ponnampalam Paramaswaami, P R Payne, R S Phillips, Madhav Mohan Rao, W H Reid, Victor Romanowski, Subramanian Shanmugam, Inder Dev Sood, R W Springhall, James Tevendale, R N Tinning, M A Turner, Madho Prashad Vaidya, Mohomad Waliuddin, A B Young

Dr Stephen Plumpton has been elected and Dr D C Hall admitted to the fellowship in dental surgery

Society of Apothecaries of London

The following diplomas have been granted

L M S S A—R J Annison, R Cook, G A Lee G H E Woodbine, Y Y Liu, C P Juniper, G Davies, H A Gordon, J E Igwe, P R S Johnson, Z F M Newton-Nowinski, R Tiru-Chelvam

M M S A—N K Allahbadia, M H Kyi, U N Pathak

D I H—G J Clarke, R H P Fernandez, N Y Prakash, A R Prasad, S Prasad, M P Y Scott, R R L Wild

Royal Society of Medicine

William Gibson research scholarship (*£200*)—Applications for this scholarship are invited from British women doctors Further particulars may be had from the secretary of the society, 1, Wimpole Street, London, W 1 The closing date for entries is May 1

International Congress of Clinical Pathology

This conference is to be held in Madrid from June 13 to 17 There is to be a section of forensic pathology with discussions on unknown causes of death with minimum visible lesions, chemical investigations in cadaver blood, and accidents in sanguineous transfusion Those who wish to contribute papers should write to Dr F E Camps, department of forensic medicine, London Hospital Medical College, Whitechapel, E 1, before Jan. 1

Applications for an Eli Lilly medical research fellowship ($300 a month for twelve months and travelling expenses) are invited from doctors registered in South Africa who wish to undertake research in the United States Further details can be obtained from Dr H A Shapiro, P O Box 1010, Johannesburg The closing date for applications is April 30

Twelve postgraduate travelling scholarships of £350 each are to be awarded by the British Commonwealth Nurses War Memorial Fund to nurses and midwives for study during 1960–61 Further particulars may be had from the secretary of the Fund, Dorset House, Stamford Street, London, S E 1

Central Middlesex Hospital research prizes (each of £50) have been awarded to Mr K Lloyd-Williams and Dr W H Summerskill

The British Dietetic Association (251, Brompton Road, London, S W 3) is offering a grant of £250 from the Rose Simmonds Fund for study or research in dietetics

A meeting of the Osler Club of London will be held on Thursday, Jan 14, at 8 15 P M , at the London School of Hygiene and Tropical Medicine, Keppel Street, London, W C 1 Prof W E Kershaw and Prof P C C Garnham will speak on the history of parasitology

Semi-permanent exhibitions will be held during the winter term at the Institute of Dermatology, Lisle Street, London, W C 2 The first, from Jan 4 to 27, will be by Dr William Frain-Bell on drug eruptions

The Ministry of Power has published its digest of statistics of pneumoconiosis in the mining and quarrying industries for 1958 Copies may be had from H M Stationery Office (3*s* 6*d*)

A revised British Standard for rubber-proofed bed sheeting fo hospital use has been published (B S 2508 1959) Copies (price 4*s*) may be obtained from the British Standards Institution, Sales Branch, 2, Park Street, London, W 1

Appointments

DE SOUZA, W D , M B Bombay orthopædic registrar, Peterborough group of hospitals

HOGARTH, T B , M B Leeds, F R C S E part-time consultant in otolaryngology, Scarborough, Bridlington, and Whitby area hospitals

KERR, W F , M B W'srand, F R C.S E senior registrar in thoracic surgery, Papworth Hospital, Cambridge

LAGOWSKI, ANATOL, M D Lwow, D A assistant anæsthetist (S H M O), Scarborough, Bridlington, Malton, and Whitby group of hospitals

LEONARD, B J , M D Manc consultant pathologist, Derby group of hospitals

PALEY, R G , M D , PH D Leeds, M R C P E consultant physician (with special interest in geriatrics), South East Northumberland, Wansbeck, Alnwick and Rathbury, and Berwick upon Tweed groups of hospitals

SOMNER, A R , M D Edin , M R C P E consultant chest physician, South East Northumberland and Newcastle upon Tyne groups of hospitals

The Hospital for Sick Children, Great Ormond Street, London

BRUCE, A W , M B Aberd , F R C S E surgical outpatient assistant
EVANS, RACHEL G , M B Lond house-physician
INALL, J A , M B Sydney, D C H house-physician
SIMPKISS, M J , M B Birm , M R C.P resident assistant physician
TALWALKER, V C , M B Bombay house-surgeon

South-Eastern Regional Hospital Board, Scotland

CONACHER, W D H , M B Glasg , M R C P E consultant physician, West Lothian group hospitals

HORTON, JEAN M , M B Lond , F F A R C S , D A consultant anæsthetist, department of surgical neurology, Western General Hospital, Edinburgh, and Edinburgh Royal Infirmary

LAIDLAW, JOHN, M B Edin , M R C P E clinical neurophysiologist (S H M O), department of surgical neurology, Edinburgh

PETRIE, P W R , O B E , M B Edin , D T M & H , D P H assistant S A M O to the Board

SMITH, A W M , M B Edin , M R C P E consultant physician, Fife area hospitals

Welsh Regional Hospital Board

DAVIES, T S , M R C.S , D P M consultant in mental deficiency and medical superintendent, Llanfrechfa Grange, near Cwnbran

LEITCH, G B , M B Dubl , F R C S E , D L O consultant E N T surgeon based at Royal Gwent Hospital, Newport

PACKER, R E , M B , B SC Wales, D O M S consultant ophthalmologist, Glantawe H M C area

THOMAS, T J , M R C S , D M R D consultant radiologist, Merthyr and Aberdare H M C

Colonial Appointments

BLENKINSOPP, E M , M R C S district M O , St Vincent
DAWSON, I E , M B Glasg medical superintendent Zanzibar
FISHER, P W , M B Cantab M O , South Pacific health service
GOULDING, M D , M B Madras, D T M & H registrar, health department, Trinidad
GUY, W D , M B Glasg M O , Northern Region, Nigeria.
HURLEY, D W H , M B N U I , F R C.S surgeon specialist, Zanzibar
LOCKHART, J D F , M B Dubl M O , Kenya
MUSSON, FRANCES A , M R C.S M O , Northern Region, Nigeria
TRUELSON, KAREN E T , M D Copenhagen, M P H M O H , Northern Region, Nigeria

Births, Marriages, Deaths

DEATHS

TURNBULL.—On Dec 23, after a short illness Dr Peter Mortimer Turnbull M C , M B , of 63, Woodbourne Avenue, Streatham, S W 16, late medical superintendent of Tooting Bec Hospital, aged 80

The Lancet · Saturday 9 January 1960

A PLACE FOR HISTAMINE IN NORMAL PHYSIOLOGY *

GEORG KAHLSON
M D Munich and Lund, Hon M D Oslo
PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF LUND, SWEDEN

UNTIL very recently studies on histamine were mainly concerned with its distribution, liberation, origin, and mode of binding This " static " approach to the problem, imposed by limitations in available methods, has led to the present impasse in the interpretation of the physiological significance of histamine A more dynamic approach would place less emphasis on the content than on the rate of formation, the rapidity of turnover, or the rate of " usage " of the amine In Lund our interest was first turned in this direction by the observation that cats could be starved to the extreme without any concomitant change in the content and distribution of histamine (Haeger and Kahlson 1952) Even removal of the pituitary gland or adrenals did not cause such changes (Haeger, Jacobsohn, and Kahlson 1952) Complete inhibition of the histamine-destroying enzyme histaminase did not influence the tissue content of histamine (Kahlson, Rosengren, and Westling 1958a) We further found evidence of a kind of regulatory mechanism designed to keep constant the tissue level of histamine in the gastrointestinal tract (Haeger, Kahlson, and Westling 1953) All this suggested that the actual tissue content of histamine is a poor indicator of changes in the metabolism of the amine Consequently we decided to study the spontaneous liberation and rate of formation of histamine under various physiological conditions

The Origin of Histamine

No methods are available for the accurate estimation of the small changes in the histamine level of blood or plasma which might possibly occur in physiological conditions

Gaddum (1951) and his colleagues suggested that estimation of histamine in the urine is more likely to give information about the release of histamine in the body than investigations on blood But this approach is limited by the fact that the food commonly eaten by man and laboratory animals contains substantial amounts of histamine, part of which is excreted in the urine Further, with such a diet intestinal bacteria decarboxylate histidine to histamine, so adding more exogenous histamine Large amounts of urinary histamine derived from exogenous sources are likely to conceal increases in urinary histamine derived from increased production or spontaneous release of endogenous histamine

The complications due to exogenous histamine can be overcome With two colleagues (Gustafsson, Kahlson, and Rosengren 1957) I investigated the distribution and urinary excretion in germ-free-reared rats fed on a special histamine-free diet, and compared these results with those from ordinary rats fed on the same diet The distribution and urinary excretion of histamine were largely identical in the two groups of rats, indicating that, when the histamine-free diet is given, the histamine excreted and contained in the tissues is endogenous in origin both in germ-free and normal animals In the male rat urinary histamine is mainly in the conjugated form In the female rat, fortunately, the urinary histamine is almost exclusively in the free, biologically active form, which allows assay directly on the isolated ileum of the guineapig The urinary excretion in what I shall call our " standard rat " thus provides a useful baseline for our studies, and I shall show by further experiments that in this rat the urinary excretion of histamine runs parallel with the rate of formation

Inhibition of Histamine Formation in Vivo

Until recently no means were known for measuring in vivo the rate of histamine formation Studies of the urinary histamine in the female rat, measured by the isotopic methods devised by Schayer (1959) have so far proved most useful (Indeed Schayer's work has contributed decisively to a new era in histamine research) The isotopic method depends principally on the injection of ^{14}C-histidine and measurement of ^{14}C-histamine and its metabolites excreted in the urine In the female rat diamine oxidase (histaminase) is the main histamine-destroying enzyme, and aminoguanidine is its specific inhibitor Under the influence of aminoguanidine a larger proportion of the histamine formed will be excreted in the urine

Histidine decarboxylase, the enzyme which converts histidine to histamine, can be inhibited in vitro by semicarbazide, but this inhibition is neither very strong nor specific. Miss Rosengren and I have injected our standard rat with semicarbazide in gradually increasing doses, and studied the urinary histamine output over periods of days or weeks For the first day or two the urinary histamine is lowered, and then, despite the sustained influence of the inhibitor, the original histamine output is restored When the injections are discontinued, however, the urinary histamine rises far above normal values, suggesting that the enzyme inhibition is overridden by the simultaneous formation of new molecules of histidine decarboxylase We were able to overcome this " escape " from the influence of the inhibitor by feeding the standard rat on a diet deficient in pyridoxine, a coenzyme of histidine decarboxylase On this diet semicarbazide in gradually increasing doses reduces the histamine formation to as little as 20% of normal (fig 1), the animal appeared fairly fit as regards appetite, exercise, and maintenance of body-weight When semicarbazide is discontinued the striking increase in urinary histamine reflects the overshoot in histamine formation The histamine content of the skin of the back, abdomen, and ears was examined before and at the time of greatest inhibition of histamine formation The two sets of figures did not differ, and they show the lack of correlation between content and rate of formation in the skin This inconsistency can be accounted for by assuming that all binding sites are occupied and that the histamine molecules are held there even when histamine is formed at a very low rate If this is true, then even a strong histamine inhibitor is unlikely to counteract the adverse effects of histamine liberated in anaphylaxis or allergy Measures aimed at hindering or tightening the coupling of histamine to the binding sites seems, a priori more promising as a remedial approach Cortisone seems to hinder the coupling of histamine to the binding sites (Schayer 1956)

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* A lecture (abbreviated) delivered in the department of pharmacology of Oxford University, in May, 1959, and at the University of Liverpool, in November, 1959

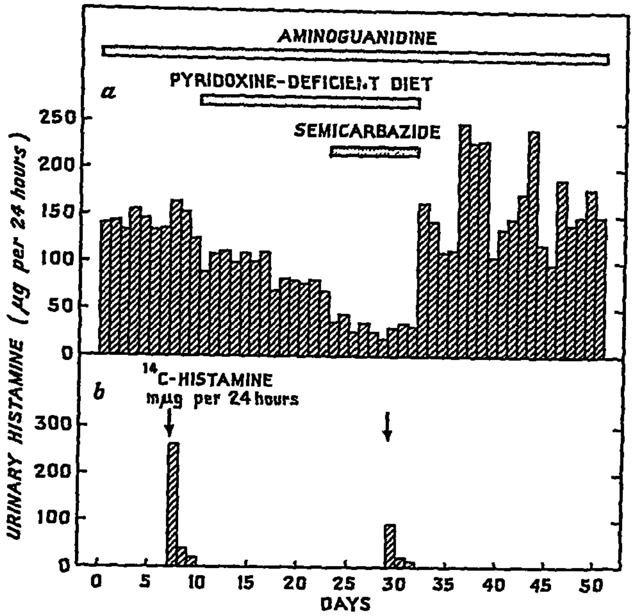

Fig 1—Female rat fed on a specially compounded histamine-free diet (*a*) Urinary excretion of free histamine (*b*) Excretion of ^{14}C-histamine in 0 001 μg (mμg) after subcutaneous injection of 220 μg ^{14}C-histidine (1 mg per kg)

Throughout the experiment the rat was under the influence of the histaminase inhibitor aminoguanidine Pyridoxine was omitted *from the diet from the 10th to 32nd day Semicarbazide was injected* subcutaneously on the 23rd to 32nd days (1st day 50 mg per kg twice daily, and 2nd day onwards 75 mg per kg twice daily)

Antihistamines do not affect the binding sites for histamine, which are different entities from the receptors through which the effects of liberated histamine on smooth muscle and glands are elicited

Histamine in Pregnancy

Increased Formation of Histamine

The basic observations on histamine formation in pregnancy are represented in fig 2 In the rat abundant production of histamine starts on the 15th day of pregnancy, as indicated by the rise in urinary excretion A peak is reached about a day before term, and then, within about 24 hours, the formation of histamine subsides to the prepregnancy level (Kahlson et al 1958a) If the fœtuses are removed surgically, without interfering with the other products of pregnancy, the rapid histamine formation promptly ceases (Kahlson, Rosengren, Westling, and White 1958b)

To establish which fœtal tissue is responsible for histamine formation, and to assess the rate of production, we incubated various tissues in vitro with radioactive histidine, and measured the ^{14}C-histamine formed The table shows that the liver produces histamine at an enormously high rate The histamine-forming capacity per gramme of tissue is about a hundred times higher in the liver than in most other tissues Even the stomach wall, which in the adult rat is the most potent manufacturer of histamine, is considerably less active per unit weight than the fœtal liver, and a mast-cell tumour of a dog, investigated in our laboratory (Lindell et al 1959), was about a hundred times less active in forming histamine In the fœtus about 80% of the total histamine formation takes place in the liver The day before term the urinary excretion of histamine falls, and within a short time—i e, 2–3 days—the histidine-decarboxylase activity of the liver regresses from an unparalleled height to the low level found in the newborn and adult animal (see table) (Kahlson, Rosengren, and White 1959)

Absence of Mast Cells and Type of Binding

Mast cells were not found in the fœtal tissues examined except for the skin

In adult animal tissues, histamine is not easily extracted unless drastic procedures which destroy cell structures are used In the fœtus the situation is entirely different The histamine so abundantly formed diffuses freely into the surrounding fluid When fœtal-tissue suspensions were incubated with ^{14}C-histidine and centrifuged, about 85% of the ^{14}C-histamine formed was in the supernatant fluid Fœtal tissues bind histamine only loosely, contain little, and produce it at a high rate, hence they are subjected to histamine in a state of rapid turnover (Kahlson et al 1959)

Histamine Formation in the Human Fœtus

We have investigated the fœtal histamine formation in man and found evidence that it is considerable (Kahlson et al 1959) Our knowledge of the mechanism is not yet as complete in man as it is in the rat In human pregnancies terminated on psychiatric grounds, we investigated the histamine content of the maternal and fœtal blood With the fœtus (weight 90–285 g) in utero at cæsarean section blood was collected from an umbilical artery The fœtus was then removed and blood was withdrawn from a carotid artery Blood was also collected from the umbilical vessels of healthy women at term Whereas fœtal carotid-artery and umbilical-artery plasma contained histamine in measurable amounts, the maternal plasma did not The umbilical-vein plasma contained less, and this difference is likely to result from diffusion between fœtal and maternal blood in the placenta

The Status of Histaminase

The striking increase in histaminolytic activity that can be shown in vitro in plasma from pregnant women is the first and only generally accepted record of a major change in histamine metabolism in normal physiology

The role of blood histaminase in pregnancy, always obscure, has become even more so on closer examination Some years

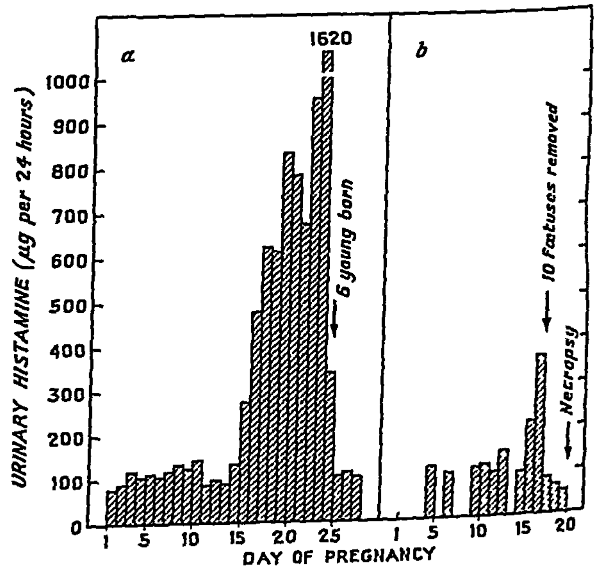

Fig 2—Urinary excretion of histamine (*a*) in a normal pregnant rat and (*b*) in a rat from which the fœtuses were removed at the *17th day of gestation*

Aminoguanidine was given throughout (From Kahlson et al [1958b], by permission of the editorial board of the *Journal of Physiology*)

THE RATE OF IN-VITRO HISTAMINE FORMATION BY VARIOUS ORGANS OF RAT FŒTUSES (AT THE 19TH AND 21ST DAY OF GESTATION), NEWBORN (WITHIN 3 HOURS OF BIRTH), 2-DAY-OLD YOUNG, AND ADULTS

Tissue	19-day litter	21-day litter	Newborn	Young	Pregnant adult
Total body		340	76–970	15	
Liver	14,000 (*23,000*)	2280		5–40	5
Lungs	1900	150		5	90–150
Heart		140		0	
Kidneys		190		0	<5
Gastrointestinal tract		150			
Brain	10	20		0	
"Rest of the body" (muscle, skin, bone)	130 (*220*)	70		30	
Stomach	2800				370–980

The figures represent ^{14}C-histamine formed in 3 hours from ^{14}C-*l*-histidine expressed as counts per min per g of tissue. 1 µg ^{14}C-histamine gives 600 counts per min The results for the organs were obtained by pooling the tissues in each litter The figures in parentheses are the mean determinations in three litters The other figures in the first column are from the same litter

ago Carlsten and Wood (1951) noticed in cats that transfer of large amounts of histaminase from the kidneys and intestinal mucosa via the lymphatics into the blood-stream, as a result of adrenalectomy, did not cause a measurable increase in blood-histaminase activity The active enzyme disappeared rapidly from the blood

Lindell et al (1958) have reinvestigated, by isotopic methods, the problem of histaminase in human pregnancy They studied in vivo the metabolism of injected ^{14}C-histamine in pregnant and non-pregnant women. The urinary pattern of the various metabolic products of injected ^{14}C-histamine showed no evidence that histaminase took a substantially greater part in the metabolism of histamine in pregnant than in non-pregnant women That is to say that the high in-vitro histaminase activity of the placenta and blood-plasma in pregnancy does not contribute in vivo to the inactivation of injected histamine This finding explains why there is no difference in the sensitivity of pregnant and non-pregnant women to injected histamine judged by the magnitude of the responses so far studied. It should not be taken to indicate that the strong histaminolytic activity in various tissues in vitro represents biochemical or experimental artefacts For example, it has been shown repeatedly that in our standard rat the urinary excretion of histamine increases two or three times under the influence of the histaminase inhibitor aminoguanidine The whole problem of histaminase is complex. Studies on histaminase have so far contributed little if anything to our understanding of the physiological significance of histamine, in contrast to what we have learnt from the effect of cholinesterase on acetylcholine

Resistance in Pregnancy to Histamine-induced Gastric Ulcer

During pregnancy rats are exposed to histamine to an extent which in the non-pregnant animal induces gastric ulcers An average litter of rat fœtuses produces, towards the end of pregnancy, more histamine in 24 hours than is present in the mother rat About 2–6 mg of fœtal histamine enters the maternal rat circulation in 24 hours A mere fraction of this amount, when mobilised from the non-pregnant animal's own stores by the injection of a histamine liberator, causes ulceration of the glandular part of the stomach (Franco-Browder et al 1959) Injections of long-acting histamine in beeswax produced ulcers in the stomach and duodenal mucosa in the eight species studied by Hay et al (1942) Thus pregnancy seems to protect the stomach against histamine-induced ulceration Clinical colleagues tell me that peptic ulcers are rarely seen and that manifest ulcers tend to heal in pregnant women The pregnant rat seems to be ideal for studying the way in which the stomach is protected from ulceration (Incidentally the strong claim for histamine as the final link in the physiological chain of events stimulating acid gastric secretion should be mentioned Gastrin appears to liberate histamine [Emmelin and Kahlson 1944, Kahlson 1948, Smith 1954] ^{14}C-histamine, deposited after injection of ^{14}C-histidine, is released in the rat's stomach on feeding [Schayer and Ivy 1957, 1958]) Here we are concerned with non-mast-cell histamine, since these cells are few or absent in the glandular gastric mucosa (Riley and West 1956)

Speculations on the Significance of Increased Histamine Formation

One can do little more than guess the meaning of the rapid histamine formation observed in pregnancy If we knew of major changes in the rat fœtus at the 15th day of gestation and the day before term (the days of onset and decline of the changes in the histamine-forming capacity) this would give a clue The smooth muscle of the uterus, which is subjected to mechanical stimulation by distension during the period of rapid growth of the fœtuses, does not contract before term The uterine muscle seems to be inhibited in some way, and such inhibition may originate from fœtal histamine This period coincides largely with that of increased histamine formation In the rat histamine inhibits the smooth muscle of the uterus and may well provide the requisite block Even the cessation of histamine formation before parturition appears to be appropriately timed This view is being tested by finding to what extent long-acting histamine in beeswax deposited under the skin postpones parturition

In no other species so far investigated does histamine inhibit uterine motility In these species the function of fœtal histamine formation must be different from that in the rat My colleagues and I thought that histamine formation in the fœtus might somehow be related to the general process of growth, and this idea can be examined

Histamine and Growth

Histamine Formation in the Regenerating Liver

The growth of the regenerating liver is particularly relevant to our study, because, like fœtal growth, its rate is very rapid In the rat the median and left lateral lobes of the liver, amounting to about two-thirds in weight, can be removed This operation has little obvious effect on the rat The remnant grows and reaches the size of the normal liver within 20 days The rate of growth is particularly rapid during the first few days after operation (see Harkness 1957)

In partially hepatectomised rats Miss Rosengren and I found that the rate of histamine formation is considerably increased during the phase of liver regeneration The rate of formation is particularly high during the first week when the growth is rapid When radioactive histidine was injected, so that histamine was formed, decarboxylation took place faster during liver regeneration than before operation The rate of histamine formation subsided when the regenerative growth was completed We found no mast cells in the regenerating liver tissues

Histamine Formation and Wound Healing

The results on the liver encouraged us to explore the possible involvement of histamine in a third type of growth—namely, wound healing At our institute a method has been devised by which the tensile strength of healing wounds can be measured Working with Dr B Zederfeldt on rats, we found that repeated injections of the histamine liberator 48/80 considerably increased the tensile strength of healing skin incisions Since Schayer et al (1959) demonstrated that 48/80, with the mobilisation of histamine, causes a great increase in the histidine-decarboxylase activity of rat skin, we have recognised that the augmented tensile strength of the wound may be linked with an accelerated formation of histamine We have also made measurements in rats in which histamine formation was inhibited by the combination of a pyridoxine-deficient diet and semicarbazide In these experiments the tensile strength of healing skin incisions was greatly reduced In the few experiments we have made so far at the time of "overshoot" in the rate of histamine formation after a period of inhibition, the tensile strength has been considerably increased The connection between histamine formation and constructive metabolism in healing wounds is so close as to be reciprocal At some later stage of knowledge this relation may be useful in medical practice

Enzyme Inhibition and Fœtal Development

The chain of evidence associating histamine-forming capacity with the general processes of growth and repair would be complete if one could show that these processes were impaired as a consequence of inhibition of histamine formation As I stated earlier, no specific inhibitors of histidine decarboxylase are available as yet But the combination of the inhibitory effects on this enzyme of pyridoxine deficiency and semicarbazide will reduce the rate of histamine formation to a very low level Miss Rosengren and I have investigated the effect of this type of enzyme inhibition on fœtal development in the rat

In one group of rats fed on a pyridoxine-deficient diet, semicarbazide was given for 8 days from the 7th day of pregnancy—that is at about the time of implantation of the ovum On examining the uterine contents at the 19th day (when the weight of a normal fœtus is about 2 g), the fœtuses were dead, being reduced to a tiny mass of disintegrated material, and the placentæ were small and in a state of regression.

In a second group of rats, also fed on a pyridoxine-deficient diet, semicarbazide was given for 8 days from the 15th day of pregnancy When the animals were killed on the 22nd day the findings were much the same as in the first group, the fœtuses were dead and mummified, and their growth seemed to have been arrested at about the 17th day—i e , when enzyme inhibition was greatest Supporting evidence has been obtained in another group of rats in which injections of the inhibitor were started at the 17th day

In controls fed on the deficient diet or injected with semicarbazide only no abnormalities in the course of pregnancy and fœtal development were noted (Kahlson and Rosengren 1959)

Thus, after reaching a more advanced stage of development, at about the day before term, fœtal growth seems to depend no longer on a high histamine-forming capacity As shown in fig 2 and the table, histamine formation regresses at about 24 hours before term to the non-pregnant level Accordingly we have found that living young of normal weight are born when enzyme inhibition is instituted during the last days of pregnancy

Semicarbazide, which is recognised as a carbonyl reacting agent, is known to inhibit a wide variety of enzymes, such as various aminoacid decarboxylases and amine oxidases, among them histaminase None of the agents whose formation is known to be inhibited by semicarbazide, has so far been found to be specifically related to fœtal development We have found that complete inhibition of diamine oxidase by aminoguanidine has no effect on the course of pregnancy or the fitness of the newborn (Kahlson et al 1958a) Further, Dr G B West and Dr H Westling have shown that the formation of 5-hydroxytryptamine is not increased in the rat during pregnancy Lastly, semicarbazide in doses larger than were used in our experiments did not inhibit the endogenous formation of 5-hydroxytryptamine in the guineapig (Weissbach et al 1957) Thus it seems reasonable to assume that the inhibition of fœtal development caused by semicarbazide is due to inhibition of histidine decarboxylase as shown by the measurable decrease in urinary histamine Final proof of this assumption will have to await the finding of specific non-toxic inhibitors of histidine decarboxylase The discovery of a rich source of the enzyme—the fœtal rat liver—is likely to boost the search for a specific inhibitor

Histamine Metabolism of the Brain

Prof Geoffrey Harris, Dr Dora Jacobsohn, and I (1952) showed that the parts of the brain functionally related to the anterior-pituitary gland, the hypothalamus, and the median eminence contained large amounts of histamine, whereas other parts of the brain examined contained very little My colleague Dr White (1959), who has now studied in vitro the formation and catabolism of histamine in brain tissue, using Schayer's isotope-dilution technique, finds that the hypothalamus forms histamine much faster than other parts of the brain

Our findings in 1952 induced Miss Fuche and me to investigate the effect of small "physiological" quantities of histamine on the secretory activity of the anterior-pituitary gland You will recall that Harris and Jacobsohn (1952), in classical experiments, showed that the anterior-pituitary gland depends for its proper function not on nervous but on vascular connections with those regions in which we found histamine in abundance Miss Fuche and I (1957) noted in rabbits in which the adrenal medulla had been destroyed that the intravenous infusion of as little as 50 µg per kg of histamine caused a significant lymphopenic response which in time, course, and pattern was identical with the response to injected corticotrophin This response to histamine was absent after hypophysectomy As a result of this work histamine is included among the possible chemical mediators of the cerebral control of the anterior-pituitary gland In exploring the physiological functions of histamine we again encounter non-mast-cell histamine The brain has no mast cells (Riley 1959)

Histamine in Muscular Exercise and Hypoxia

When histamine was brought on the physiological scene, it was thought to be responsible for the vasodilatation of contracting skeletal muscle and for the phenomenon of reactive hyperæmia Thomas Lewis cautiously introduced the term "H-substance" for this agent But Anrep, who contributed brilliantly to knowledge in this field by his studies on the nature of urinary histamine (in which he measured the arteriovenous histamine difference in muscles at work and skin in oxygen-lack), claimed identity of the hypothetical H-substance with histamine. After histamine had thus been brought into the limelight, many investigators set out to assess its role in reactive vasodilatation Much was written on the subject from many parts of the world In Lund we have worked hard in this field, and I was privileged to study the problem in Cairo under the guidance of the late Professor Anrep But, despite all this effort, the consensus of current opinion is that histamine has not with certainty been shown to play a part in any of the various kinds of reactive hyperæmia so far investigated

Oxygen-lack is well known to affect the small blood-vessels directly, dilating them as in reactive hyperæmia, and so it seemed appropriate to examine the output of histamine in this condition In experiments made in collaboration with Miss Rosengren, our standard rats were exposed to hypoxia in the low-pressure chamber of our subdivision of Aviation Physiology The chamber was evacuated to a pressure of about 6000 m, with an oxygen content of 45% of that at sea-level In the chamber the rats showed signs of oxygen-lack. Urine was collected in 24-hour periods Under the influence of hypoxia the rate of histamine formation was reduced to roughly half of normal If mobilisation of histamine were concerned in the reactive hyperæmia of oxygen-lack, the reverse should have happened The experiments so far made are only preliminary and merely show that histamine is in some way involved We plan to study in greater detail the nature of the underlying changes in histamine metabolism

Concluding Remarks

To those, like myself, who have been trying to find a simple and clear cause-and-effect relation in which histamine acts as a direct stimulus to and controller of effector cells (such as smooth muscle, blood-vessels, and glands) the present findings may seem bewildering It now appears, however, that the histamine-forming capacity is in some way connected with the metabolic machinery common to the anabolic processes of development, growth, and repair The situation is complex and we cannot yet say whether the observed changes in the rate of histamine formation are essential to the events studied or whether they are the outcome of a different primary physiological reaction In exploring the role of histamine in normal physiology, further work on the inhibition of histamine formation and its consequences in the animal seems particularly promising, especially in relation to fœtal development

Through the veil two facts emerge with considerable certainty

1 Histamine, as linked with the physiological events at present being studied, is not formed from mast cells

2 As far as physiology is concerned, studies of the rate of histamine formation are more promising than the measurement of histamine content.

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CONTROL OF LIPÆMIA IN CHILDREN WITH DIABETES MELLITUS

THE ROLE OF INSULIN AND THE EFFECTS OF A DIET RICH IN UNSATURATED FATTY ACIDS

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IN an earlier publication (Wolff and Salt 1958) it was noted that initially high levels of β-lipoprotein lipid in the serum of untreated diabetic children were rapidly lowered by treatment with insulin Moreover, in a group of children under good or fair diabetic control, the mean levels of β-lipoprotein lipid, cholesterol, and esterified fatty acid in the serum were higher in patients with blood-sugar levels above 200 mg per 100 ml than in those with levels below 200 mg It was suggested that high levels of certain serum lipids might be at least partly responsible for the early onset of vascular complications in the young diabetic

In the present study we have attempted to define the effects of insulin on the various serum lipids Further, in a number of patients already under insulin control, we have studied the diurnal variation of serum lipids to determine how closely blood-sugar and the lipids are related

In practice, one cannot expect that blood-sugar control will be maintained through the years strictly enough to keep the serum lipids always at a minimum For this reason we have investigated, in these diabetic children, the effects of a diet rich in unsaturated fatty acid esters

In a preliminary experiment an emulsion of sunflower-seed oil was given in substitution for some of the animal fat of the ordinary diets Later, more success was obtained with foodstuffs whose fat was largely composed of corn (maize) oil. When these were given in strict isocaloric exchange with animal fat of the usual diet, certain serum-lipid concentrations were lowered to levels not attainable with insulin alone, and these low levels were maintained even when insulin therapy was somewhat relaxed

In view of the possible causal relation between elevation of the serum lipids and the early onset of vascular complications in the diabetic patient, these findings may have practical importance

The Investigation

Our fourteen patients were between the ages of 2 and 14, with diabetes mellitus of varying duration Four of them, hitherto untreated, were studied to reveal changes in the serum lipids when insulin treatment was first begun In four already under insulin control diurnal variation of the serum lipids was studied Eight under insulin control were fed sunflower-seed oil emulsion, five other patients were given a diet containing corn oil

In preliminary experiments, the usual dietary fat was reduced and a 50% emulsion of sunflower-seed oil in water, suitably flavoured, was given thrice daily The daily

TABLE I—BLOOD-SUGAR AND SERUM-LIPID LEVELS IN FOUR PREVIOUSLY UNTREATED PATIENTS DURING THE FIRST PHASE OF INSULIN THERAPY

Patient	Hours after insulin therapy begun	Blood-sugar (mg per 100 ml)	Serum lipid (mg per 100 ml)									Total lipid
			Cholesterol		Phospholipid	Triglyceride	Total Esterified fatty acid	Lipoprotein lipid fractions				
			Esterified	Unesterified				ω	β	α	Ratio β α	
A	0	645	110	44	234	412	621	45	1050	185	5 7	1280
	4	376	194	68	264	134	433	66	689	165	4 2	920
	17	302	127	46	143	83	259	65	448	87	5 1	600
	25	60	119	57	169	27	218	91	412	157	2 6	660
	42	498	115	57	200	118	322	73	376	131	2 9	580
B	0	680	210	67	322	158	508	159	529	322	1 6	1010
	16	388	174	67	255	91	373	135	435	290	1 5	860
	42	220	162	57	260	93	373	107	513	260	2·0	880
C	0	578	159	67	311	344	642	104	666	270	2·5	1040
	17	285	121	47	196	129	316	70	365	205	1 8	640
	68	249	134	47	222	184	413	213	394	213	1 8	820
D	0	440	133	65	281	485	738	343	605	172	3 5	1120
	19	304	141	65	216	214	442	233	419	148	2 8	800
	43	416	126	49	203	155	367	131	402	197	2·0	730
Normal range		60–160	85–175	35–75	160–310	0–200	190–450	0–120	300–580	150–280	1 6–3 0	460–860

amount of 50 g oil contained about 30 g linoleic acid as the main unsaturated (dienoic) fatty acid

In later experiments, the diets contained special milk, margarine, and cheese-spread, all made with corn (maize) oil instead of animal fat Corn oil contains about half its weight of linoleic acid as the main unsaturated fatty acid The diets were arranged to contain 50 g corn oil per day for the older children and 40 g for the younger, as well as known amounts of protein (40 to 60 g) and carbohydrate (170 to 230 g) graded according to age The quantities of corn oil, together with 15 g other dietary (animal) fat, replaced the total animal fat included in the control diets given before and after the periods of corn-oil feeding The protein and carbohydrate contents of the corn-oil and control diets were kept constant for each patient throughout the experiments

In three patients fat-balance studies for periods of 3 days showed normal fat absorption on the corn-oil diet

Blood-sugar was estimated by the Folin-Wu micro-technique, using unlaked blood in Herbert and Bourne's method (Harrison 1937)

Serum lipoprotein was separated electrophoretically on absorbent paper into ω, β, and α fractions, after staining with oil red O these fractions were estimated on a relative basis by the method described by Salt and Wolff (1957) The fractions were calculated as absolute concentrations by reference to the serum total-lipid concentrations determined by the method of de la Huerga et al (1953)

Analyses of sera for esterified cholesterol and unesterified cholesterol (Schoenheimer and Sperry 1934), lipid phosphorus (method adapted from Gomori 1942) and total esterified fatty acid (Stern and Shapiro 1953) were also made

In calculations, a representative molecular weight of 277 2 was used for fatty acid, phospholipid (M W 806) was obtained by lipid phosphorus ×26, triglyceride was computed by difference calculation.

Results

Effects of Insulin on Hyperlipæmia

Table I shows the effects of insulin on the serum lipids and lipoproteins in four previously untreated patients They were all conscious on admission, patient A was drowsy and she was the only one who was dehydrated Ketonuria was present in patients A, B, and D

Under insulin the high values for serum total-lipid, esterified fatty acid, triglyceride, phospholipid, and β-lipoprotein lipid were lowered to normal within 24 or 48 hours The α-lipoprotein lipid fraction showed little change, raised β/α ratios decreased rapidly No uniform change occurred in the serum-cholesterol levels In three cases these were already normal, in patient B, in whom the concentration was initially high, it was brought down to normal In patients B and D the initially high ω-fraction became normal

In patient A the β-lipoprotein was very high at first but the ω fraction was not raised and the serum was optically clear As the serum-cholesterol and phospholipid values were normal but the triglyceride markedly raised, we conclude that the high β fraction resulted from accumulation within it of triglyceride In patient C the findings were similar, though the hyperlipæmia was less In patient D the excess triglyceride was largely in the form of chylomicrons (ω fraction), and the serum was turbid

The observations suggest that, in these untreated diabetic children, an initial excess of triglyceride was usually and mainly responsible for the hyperlipæmia, and was present either in the β-lipoprotein complex or in the form of chylomicrons (ω fraction) Insulin treatment rapidly lowered the raised triglyceride levels irrespective of whether the excess was in the ω- or β-lipoprotein fractions

Diurnal Variations in Serum Lipids

We next tried to determine whether there was any relation between blood-sugar levels and any of the serum lipids during a 24-hour period in patients in whom diabetic control had already been established

Blood specimens were so timed as to avoid postprandial elevations of serum triglyceride In one patient, blood-sugar and the various serum lipids were estimated at 4 separate times, spaced at intervals between 7 A M and midnight, on 4 different days The widest variation in diurnal blood-sugar observed was from 52 to 384 mg per 100 ml On this day, as on the other occasions, the diurnal variation in all the lipid fractions was trivial In this patient on a later occasion, and in three other patients, comparable observations of blood-sugar and serum-lipid concentrations were made just before and 3 hours after the midday meal

The results confirmed the diurnal constancy of the lipid levels

Effects of Unsaturated Fats

Sunflower-seed oil —The effects of this oil on serum-lipid concentrations were studied in eight diabetic children already under established control with insulin The first trial extended over 28 days while the patient was in hospital and the unsaturated dietary fat was given in place of an equal amount of the usual (largely animal) dietary fat Initially the serum lipids were all within the normal range The effect of the oil feeding, observed at 14 days, was a lowering of the serum esterified-cholesterol and β-lipoprotein-lipid concentrations. At 28 days the lower levels were maintained.

This patient on a later occasion, and seven others, were fed sunflower-seed oil at home for periods of 22 to 42 days. Under home conditions there was some uncertainty about the maintenance of the diet, and in some patients the insulin dosage had to be increased a little during the trial. These factors may have led to less clear results. However, the serum β-lipoprotein lipid fell in every patient, and the esterified cholesterol fell in most of those whose initial levels were not already low. On a mean basis, serum β-lipoprotein, esterified fatty acid, and phospholipid were lowered to about 80% of the initial levels, esterified cholesterol to about 90%, and triglyceride to about 60%. When sunflower-seed oil feeding was discontinued, all these lipids reverted to previous levels.

Corn oil.—Table II shows the effects of the corn-oil diet on the serum lipids in five patients.

The blood specimens were taken at noon, before the midday meal, so that alimentary lipæmia would not complicate the findings. The ranges and mean values for the serum-lipid concentrations are given only for periods when steady levels had been achieved with the different diets. Analytical values were also recorded for the transition periods but are excluded from the calculations.

In patients B and D the diagnosis had been made recently, and the rapid changes induced by insulin therapy have already been described. In patient E the disease was also of short duration. In all three cases the corn-oil diet was started only after the initial hyperlipæmia had responded to insulin and the various serum lipids had reached steady levels for 1–3 weeks.

Patient F, in whom the diagnosis had been made 2 years previously, was also given the corn-oil diet. In his case evaluation of the data was complicated, because diabetic control was being improved by an increase in insulin dosage during the first control period and shortly before the change to the corn-oil diet. The increased insulin control caused a progressive fall of the blood-sugar, serum-phospholipid, triglyceride, and β-lipoprotein-lipid levels.

Patient G was newly diagnosed and was fed the corn-oil diet from the beginning of insulin therapy; consequently there was no initial control diet period. The values recorded for the corn-oil period (table II) were obtained only when insulin control had become established.

The corn-oil diet reduced esterified cholesterol and β-lipoprotein lipid to about 60% of the initial control levels, total-lipid and esterified fatty acid to about 75%, unesterified cholesterol and phospholipid to about 80%. The α fraction was lowered to about 90% and the β/α ratio to about 65% of the control levels. Serum triglyceride and the ω fraction showed no consistent change.

Two of the patients are being maintained on the corn-oil diet and the results will be reported.

In three patients (E, F, and G) the diet was changed again from corn oil to control. The effects of the isocaloric change are shown in table II. As was expected, a marked rise occurred in all the serum-lipid levels which had been lowered by the corn-oil diet, though at the end of 3 weeks some fractions had not fully regained the levels characteristic of the initial control period.

The detailed effects of the corn-oil diet are shown for patient B in fig. 1. α-lipoprotein lipid increased during the transition period while other serum-lipid levels were falling. Later, when the new equilibrium levels were reached the α fraction had fallen and reverted to the control level. In patient D similar changes were observed.

Insulin and Corn Oil

In two patients we tried to find out whether the corn oil could prevent the rise of certain serum lipids which is to be expected when diabetic control is allowed to deteriorate.

Fig. 2 shows the results for patient E, in whom insulin dosage was approximately halved for a time. Despite the corn-oil diet, when blood-sugar was elevated there was a definite rise in serum triglyceride, esterified fatty acid, and ω fraction, a slight rise in the β fraction, and a fall in the α fraction. These changes are in the opposite direction to those already described in the previously untreated patient when started on insulin therapy and they were in the same lipid fractions.

Whereas in patient E the insulin dose was decreased abruptly, in the other patient (F) the reduction was more gradual. Similar lipid changes occurred but became

TABLE II—SERUM-LIPID LEVELS IN FIVE PATIENTS UNDER INSULIN CONTROL DURING STEADY STATE PERIODS ON DIFFERENT DIETS
DATA FOR THE TRANSITION PERIODS ARE NOT INCLUDED

Patient	Diet	No of Observations	Serum-lipid, ranges and means (mg per 100 ml. serum)									
			Cholesterol		Phospholipid	Triglyceride	Total Esterified fatty acid	Lipoprotein lipid fractions				Total lipid
			Esterified	Unesterified				ω	β	α	Ratio β/α	
B	Control	4	162–191 178	63–74 67	223–292 270	41–108 72	335–405 368	58–139 106	427–555 494	184–226 208	2·03–2·95 2·40	740–920 810
	Corn-oil	2	75–87 81	50–52 51	190–234 212	36–49 43	216–254 235	67–107 87	276–278 277	197–204 201	1·36–1·40 1·38	540–590 565
D	Control	4	123–179 142	49–60 57	220–300 247	15–79 47	243–380 302	71–133 97	285–392 337	202–276 221	1·41–1·69 1·54	620–760 655
	Corn-oil	4	57–79 67	45–60 52	178–260 210	25–55 36	202–236 219	60–128 100	212–262 233	145–240 190	0·88–1·60 1·27	470–580 523
E	Control	2	149–150 150	49–58 54	250–305 278	69–71 70	335–368 352	206–263 235	338–513 426	279–301 290	1·21–1·74 1·48	880–1020 950
	Corn-oil	3	74–92 81	27–49 38	205–231 214	103–211 147	296–398 340	120–229 177	192–259 221	252–288 269	0·67–1·03 0·83	600–740 667
	Control	2	114–123 119	49–53 51	265–313 289	118–169 144	365–452 409	127–184 156	355–379 367	237–278 258	1·28–1·59 1·44	760–800 780
F	Control*	5	108–141 123	32–46 40	203–333 228	62–133 101	305–367 331	22–69 51	344–422 377	180–216 194	1·83–2·28 1·94	580–660 622
	Corn-oil	6	83–105 97	23–37 28	121–184 158	1–64 26	170–246 196	73–114 91	155–313 217	160–206 180	0·75–1·93 1·23	440–560 458
	Control	3	127–155 143	37–48 43	181–210 196	41–119 84	277–322 306	128–276 200	338–368 355	116–171 146	2·15–2·92 2·48	640–735 702
G†	Corn-oil	2	75–75 75	25–25 25	138–150 144	47–67 57	187–211 199	32–70 51	250–255 253	150–153 152	1·67–1·67 1·67	440–470 455
	Control	5	133–155 141	45–58 51	236–255 246	93–167 118	335–429 383	85–155 125	423–547 489	164–248 206	1·70–3·33 2·44	760–900 820

* Blood sugar levels were high during this period. † No initial control period available (see text).

considerable only when the blood-sugar was allowed to rise to 400 mg per 100 ml or more

In both patients serum cholesterol and phospholipid remained at the low levels characteristic of the response to the diet rich in unsaturated fats The slight rise in β-lipoprotein lipid was therefore apparently due to an increase in triglyceride contained in the β complex

Discussion

Consideration of the origin and nature of hyperlipæmia in diabetes raises questions of great importance Hyperlipæmia undoubtedly exists in the untreated patient, it is promptly moderated by insulin therapy and is induced again in the treated patient if insulin is withheld In the experiments of Hirsch et al (1953) the hyperglycæmia induced in diabetics by withholding insulin was accompanied by hyperlipæmia, this consisting mainly in an increase in serum triglyceride Harris et al (1953) described a similar abnormality in diabetic acidosis, but also noted that other fractions of the serum lipids were involved in the resultant hyperlipæmia, which in their patients was often further exaggerated by hæmoconcentration

Wolff and Salt (1958) observed that in diabetic children under established insulin control the mean levels of serum β-lipoprotein lipid, cholesterol, and esterified fatty acid were correlated with the height of the blood-sugar levels

We are inclined to direct attention to the occurrence of hyperlipæmia in patients whose diabetes, though uncomplicated by ketonuria and acidosis, is not perfectly controlled, and many, if not most patients, fall into this group Of course hyperlipæmia is likely to be greatest in extreme decontrol with acidosis and ketosis, and we may here recall that juvenile diabetes has a tendency to ketoacidosis

Strisower et al (1958) showed by ultracentrifugal fractionation that diabetics in a non-acidotic decontrol phase had mild hyperlipæmia due mainly to an increase in the S_f0-12 lipoprotein class, in diabetics with acidosis there was pronounced hyperlipæmia due to gross increases in lipoproteins of the S_f20-400 classes and this was slightly offset by depletions of the S_f0-12 class and of the high-density lipoproteins Correlations between ultracentrifugal lipoprotein classes and paper-electrophoresis fractions (Smith 1957) have helped to elucidate these observations

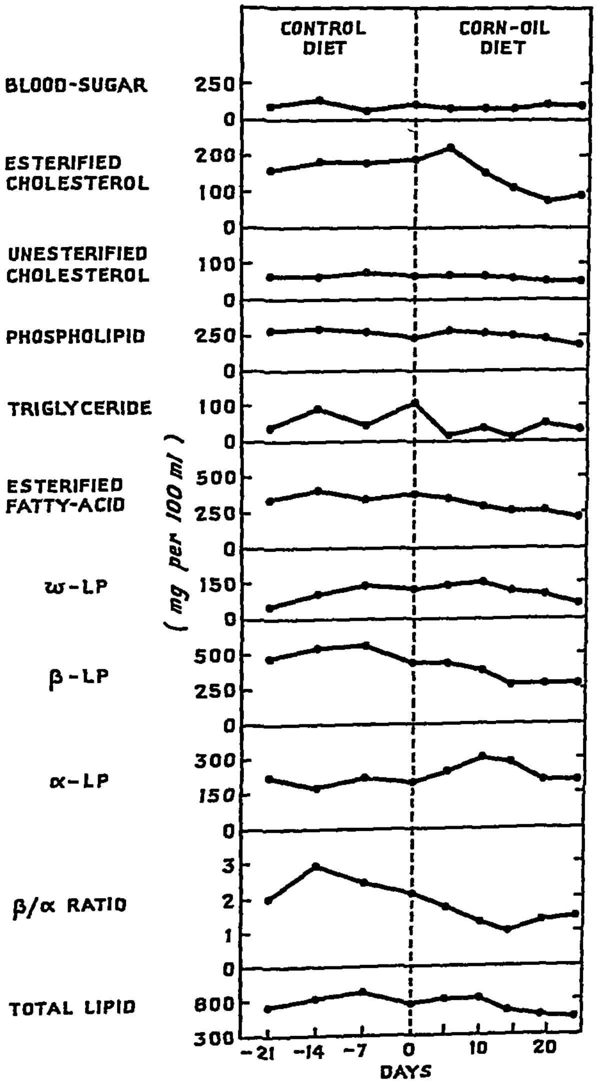

Fig 1—Effects of corn-oil diet in patient B

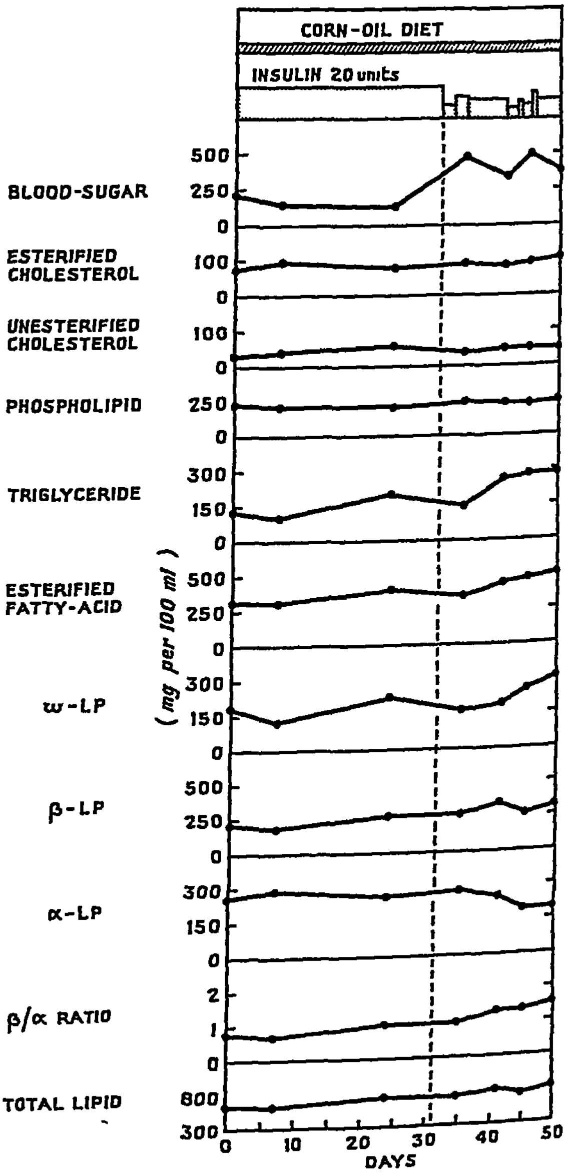

Fig 2—Effects of corn-oil in patient F

In discussing the nature and causes of diabetic hyperlipæmia, Albrink and Man (1958) stress the close relation between carbohydrate metabolism and serum-triglyceride concentration. They point out that some excess triglyceride can accumulate in the β-lipoprotein complex, the serum still being clear, but if greater amounts are present they must accumulate in the serum in particulate form. The serum is then turbid. On centrifugation at 18,000 r p m for one hour, a cream-layer (chylomicrons) separates from a clear infranatant solution. We are in agreement with these observations, but have encountered certain sera from hitherto untreated cases in which the infranatant layer was not completely clear. The nature of the material causing the opalescence is under investigation, at present we suspect that it consists of β-lipoprotein containing an excess of triglyceride.

The mechanism responsible for accumulation of triglyceride in the diabetic remains obscure, failure to clear dietary fat is likely to play a part, but endogenous sources are also undoubtedly implicated. Albrink and Man emphasise that with persistent chylomicronæmia there is an associated excess of cholesterol and phospholipid commensurate with the triglyceride. Cholesterol may further accumulate in the β-lipoprotein complex. The excess cholesterol in the diabetic is thought to originate from increased production by synthesis from acetate fragments.

Our present results confirm that hyperlipæmia in diabetic children can be diminished by adequate insulin therapy, the serum triglyceride being mainly affected, and we show that the concentrations of certain serum lipid components, notably β-lipoprotein lipid, can be further diminished by feeding an unsaturated, instead of a saturated, type of dietary fat.

When sunflower-seed oil was fed, serum β-lipoprotein, esterified fatty acid, phospholipid, esterified cholesterol, and triglyceride were lowered. (The lowering of triglyceride may perhaps have been, partly at least, a result of unavoidable increases in insulin dosage.) On the corn-oil diet, serum esterified cholesterol, unesterified cholesterol, phospholipid, esterified fatty acid, and β-lipoprotein lipid were all lowered. Similar results have been reported in adult diabetics from the feeding of safflower-seed oil (Gordon 1957) and of vegetable (nut) oil (Kinsell et al 1954).

The mechanism by which unsaturated dietary fat lowers the level of serum β-lipoprotein lipid is not clearly understood. Our observations suggest that a transfer of lipid from β- to α-lipoprotein may be an intermediate step, since α-lipoprotein was seen to rise transitorily at the time when β-lipoprotein was being lowered.

In the experiments designed to show the effects of insulin decontrol while the corn-oil diet was being fed, serum triglyceride and esterified fatty acid increased but cholesterol, phospholipid, and β-lipoprotein lipid remained low, showing that the influence of corn oil had persisted. This finding has a special significance for the diabetic in whom the disorder of carbohydrate metabolism, unless constantly well controlled, leads under usual dietary conditions to a rise in cholesterol, phospholipid, and β-lipoprotein lipid levels.

In the young diabetic prevention of vascular disease is the outstanding problem. The lipæmia of diabetes resembles in some respects that known to precede atheroma in older non-diabetic subjects. In both, the β-lipoprotein and cholesterol levels are raised, thus diabetic lipæmia could be a factor in the early development of vascular disease in the young. Though the serum lipids of diabetics can be kept within normal limits by perfect control, the practical difficulties of control are such that it is unlikely to be maintained constantly over long periods. Moreover, excessive insulin dosage must be avoided, because of the risk of hypoglycæmia, suppression of residual endogenous islet function, and development of insulin antagonists. Hence, additional control of lipæmia by dietary means demands a long-term trial.

Summary

In four previously untreated diabetic children, insulin therapy lowered the initially high values for serum triglyceride, β-lipoprotein lipid, esterified fatty acid, and phospholipid to normal within 24 or 48 hours. In one of the patients, in whom the serum-cholesterol level was initially high, insulin brought it down to normal.

In four patients under established diabetic control, observations of the diurnal variations of the various serum lipids and blood-sugar levels revealed a relative constancy of the lipid levels in the face of considerable variation in blood-sugar.

In thirteen diabetic patients under insulin control the effects of feeding unsaturated fats on the serum lipids were observed. Eight were given an emulsion of sunflower-seed oil, this led to a lowering of serum β-lipoprotein lipid, esterified fatty acid, phospholipid, esterified cholesterol, and triglyceride concentrations to levels below the control levels. Five were given a diet in which most of the usual (animal) fat had been replaced by corn oil. The isocaloric change from the control to the corn-oil diet led to a fall in esterified cholesterol and β-lipoprotein lipid to about 60% of the initial control levels, esterified fatty acid to about 75%, and unesterified cholesterol and phospholipid to about 80%.

In two patients on the corn-oil diet the effects of lessening the insulin dosage were observed. The cholesterol and phospholipid remained at low levels, but the diet did not prevent a rise in triglyceride, esterified fatty acid, and the ω (chylomicron) lipid fractions.

The hyperlipæmia of diabetes has similarities to that preceding atheroma in older non-diabetic subjects. It may play an important part in the causation of the vascular complications.

Hyperlipæmia could no doubt be prevented by perfect control of the diabetic process with insulin, but such control, however desirable, is rarely if ever maintained for long periods. As an additional controlling measure, a diet rich in unsaturated fat deserves long-term trial.

We gratefully acknowledge the help of Miss A S Fosbrooke, Mr G A Brown, and Mr B T Rudd in the analytical work, of Mr A E Marston in preparing the sunflower-seed-oil emulsions, and of Sister H R Jukes in preparing the corn-oil diets. Unilever Ltd gave us the sunflower-seed oil, and Alfonal Ltd the corn-oil foods. We are grateful also to the endowment research fund of the United Birmingham Hospitals for financial support.

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POTENTIATING EFFECT OF QUINOLINES ON THE ACTION OF TETRACYCLINE IN AMŒBIC DYSENTERY

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The usefulness of antibiotics in the treatment of amœbic dysentery is now widely accepted, and the tetracyclines have been shown to be the most valuable Tetracycline, chlortetracycline, and oxytetracycline are almost equally effective In a dosage of 1 g daily they produced in our hands immediate cure in 92–97% of cases (Elsdon-Dew et al 1952, Elsdon-Dew 1954–55) Their main disadvantages are expense, failure to prevent hepatic involvement, and a significant relapse-rate Because of this we have never claimed that tetracyclines can fully replace emetine as the treatment of choice Nevertheless these antibiotics are of great value for ambulant patients, and we now treat satisfactorily several thousand cases of amœbic dysentery each year as outpatients with tetracyclines together with diiodohydroxyquinoline.

TABLE I—RESULTS OF TREATING 50 CASES OF AMŒBIC DYSENTERY WITH TETRACYCLINE, DIIODOHYDROXYQUINOLINE, AND CHLOROQUINE

Day of assessment	10th	15th	20th	27th	Cumulative (27 days)
Success	12 (*24%*)	31 (*62%*)	44 (*88%*)	47 (*94%*)	47 (*94%*)
Probable failure	38 (*76%*)	19 (*38%*)	6 (*12%*)	0	0
Parasitic failure	0	0	0	3 (6%)	3 (6%)

In the following trial our object was to see whether effective treatment could be given at lower costs, with small doses of tetracycline We also hoped to assess the effect of giving chloroquine and/or diiodohydroxyquinoline in addition

Material and Methods

Four drug combinations were tested

1 Fifty patients were treated with tetracycline 50 mg thrice daily for 10 days, diiodohydroxyquinoline 600 mg thrice daily for 20 days, and chloroquine sulphate 800 mg immediately, followed by 400 mg 6 hours later, and then 200 mg twice daily for 14 days

TABLE II—RESULTS OF TREATING 25 CASES OF AMŒBIC DYSENTERY WITH TETRACYCLINE AND DIIODOHYDROXYQUINOLINE

Day of assessment	10th	15th	20th	27th	Cumulative (27 days)
Success	6 (*24%*)	9 (*36%*)	14 (*56%*)	15 (*60%*)	15 (*60%*)
Probable failure	17 (*68%*)	11 (*44%*)	5 (*20%*)	3 (*12%*)	3 (*12%*)
Parasitic failure	2 (*8%*)	3 (*12%*)	1 (*4%*)	1 (*4%*)	7 (*28%*)

2 Twenty-five patients had tetracycline and diiodohydroxyquinoline in the above dosage, but no chloroquine

3 Twenty-five patients were given tetracycline and chloroquine in the same dosage as the first group, but no diiodohydroxyquinoline

4 Twenty-five patients had diiodohydroxyquinoline and chloroquine in the stated dosage, but no tetracycline

All were African males complaining of diarrhœa with blood and mucus, showing ulceration on sigmoidoscopy, and with actively motile *Entamœba histolytica* in the stools and ulcer scrapings Severely ill patients, and those with complications of coexisting disease, were excluded

Sigmoidoscopy was performed on admission and on the 5th, 10th, 20th, and 27th days after starting treatment Daily stool examinations were performed

Results were classified into the following categories

1 *Success*—Symptom-free, ulcers healed, and no parasites demonstrated

2 *Probable failure*—Persistent open ulceration, but no parasites demonstrable in stools or scrapings

3 *Parasitic failure*—Amœbæ still present, with or without open ulceration

TABLE III—RESULTS OF TREATING 25 CASES OF AMŒBIC DYSENTERY WITH TETRACYCLINE AND CHLOROQUINE

Day of assessment	10th	15th	20th	27th	Cumulative (27 days)
Success	4 (*16%*)	8 (*32%*)	8 (*32%*)	12 (*48%*)	12 (*48%*)
Probable failure	15 (*60%*)	14 (*56%*)	7 (*28%*)	1 (*4%*)	1 (*4%*)
Parasitic failure	6 (*24%*)	3 (*12%*)	7 (*28%*)	2 (*8%*)	12 (*48%*)

Cases which remained or became parasitic failures on or after completing their course of treatment under trial were removed at this point and given other treatment

Results

Tables I–IV indicate that in all groups the majority of patients still had open rectal ulceration at 10 days Thereafter the ulcers tended to heal But those who received only diiodohydroxyquinoline and chloroquine (table IV) tended to relapse as soon as their treatment was completed at the end of 20 days, so that by the 27th day only 20% could be classified as successes, and the combined failure-rate was 80% The group which had tetracycline and diiodohydroxyquinoline (table II) showed only a slightly better success-rate at 27 days (60%, with a combined failure-rate of 40%) than those who had tetracycline and chloroquine (48%, with a combined failure-rate of 52%) On the other hand the group which received both diiodohydroxyquinoline and chloroquine with tetracycline showed a success-rate at 27 days of 94% and a combined failure-rate of only 6%

TABLE IV—RESULTS OF TREATING 25 CASES OF AMŒBIC DYSENTERY WITH DIIODOHYDROXYQUINOLINE AND CHLOROQUINE

Day of assessment	10th	15th	20th	27th	Cumulative (27 days)
Success	6 (*24%*)	13 (*52%*)	14 (*56%*)	5 (*20%*)	5 (*20%*)
Probable failure	15 (*60%*)	8 (*32%*)	8 (*32%*)	4 (*16%*)	4 (*16%*)
Parasitic failure	4 (*16%*)	4 (*16%*)	3 (*12%*)	13 (*52%*)	16 (*64%*)

Follow-up Studies

Follow-up was incomplete But of those patients who received all three drugs three had relapsed within a month, giving a total failure-rate of 12% Three relapsed in the tetracycline and diiodohydroxyquinoline group, and one in the tetracycline and chloroquine group, giving total

TABLE V—RESULTS OF FOLLOW-UP OF 27-DAY "SUCCESSES" 1 MONTH AFTER DISCHARGE

—	No of successes available	No who attended	No of failures	Total failure-rate
Tetracycline, diiodohydroxyquinoline, and chloroquine	47	32 (*68%*)	3 (*6%*)	*12%*
Tetracycline and diiodohydroxyquinoline	15	5 (*33%*)	3 (*20%*)	*52%*
Tetracycline and chloroquine	12	6 (*50%*)	1 (*8%*)	*56%*
Diiodohydroxyquinoline and chloroquine	5	3 (*60%*)	1 (*20%*)	*84%*

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* The Amœbiasis Research Unit is sponsored by the South African Council for Scientific and Industrial Research, the Natal Provincial Administration, the University of Natal, and the United States Public Health Service (grant E-1592)

failure-rates of 52% and 56% respectively. Of those who had diiodohydroxyquinoline and chloroquine alone one relapsed, giving a total failure-rate of 84%.

Discussion

The use of a systemic amœbicide, such as chloroquine, together with antibiotics, in the treatment of amœbic dysentery is fully justified to prevent hepatic complications. Chloroquine is valuable in hepatic amœbiasis though it has little effect in dysenteric forms of the disease. Our results, however, show a striking increase in the cure-rate when chloroquine and diiodohydroxyquinoline are given in association with suboptimal doses of tetracycline.

Armstrong et al. (1955) found that chlortetracycline in a dosage of 80 mg. daily for 10 days gave a success-rate of 63% at 10 days, but by the 27th day this had fallen to 53%, with a total failure-rate of 47%. In a further series they therefore gave a combination of chlortetracycline 100 mg. daily for 10 days, diiodohydroxyquinoline 600 mg. thrice daily for 20 days, and chloroquine 500 mg. daily for 15 days, and achieved a satisfactory success-rate of 85% at 10 days, and of 91% at 27 days, with a total failure-rate of only 6%. The improved response in this series was ascribed to the addition of diiodohydroxyquinoline, and the possible role of chloroquine was not emphasised.

The results of the present trial lead to surprising conclusions. Earlier trials of diiodohydroxyquinoline gave a success-rate of 58% at 20 days (Armstrong et al. 1949) which corresponds with the success-rate of 56% at 20 days now obtained with diiodohydroxyquinoline and chloroquine combined. In other words, the addition of chloroquine to diiodohydroxyquinoline did not affect the success-rate. Moreover, a high proportion of these patients have now been shown to relapse immediately the drugs are discontinued.

Armstrong et al. (1955) had a success-rate of 53% with small doses of chlortetracycline. We have now shown that the addition of either diiodohydroxyquinoline or chloroquine did not significantly increase the successes. But when the three drugs were used together the proportion of successes rose strikingly to 94%. This seems to indicate that tetracycline in small doses is the most effective drug, but in order to achieve a high proportion of successes the addition of both chloroquine and diiodohydroxyquinoline is necessary. Whenever dysenteric amœbiasis is treated with tetracyclines, therefore, it seems reasonable that chloroquine should be given in addition to diiodohydroxyquinoline not only to safeguard the liver but also because of the enhanced efficacy of combined therapy.

When tetracycline 1 g. daily was given for 10 days the rectal ulcers were healed in 89% of patients by the 10th day, and in 94% by the 15th day (Elsdon-Dew 1954–55). By contrast, when tetracycline 150 mg. daily was given with diiodohydroxyquinoline and chloroquine, the ulcers were healed in only 24% of patients by the 10th day, and in 62% by the 15th day. Thus when tetracycline is used in small doses the rate of healing of ulcers is considerably slower, although the end-result is satisfactory. In view of the slower clinical response and less rapid healing of ulcers tetracycline in small doses is not recommended in acute amœbic dysentery, but it may be justified sometimes where reducing the cost is vital.

Summary

Amœbic dysentery has been treated with four drug combinations:

1. Fifty cases had both chloroquine and diiodohydroxyquinoline in addition to suboptimal doses of tetracycline.
2. Twenty-five cases were given suboptimal doses of tetracycline with diiodohydroxyquinoline.
3. Twenty-five cases had suboptimal doses of tetracycline with chloroquine.
4. Twenty-five cases were given diiodohydroxyquinoline and chloroquine.

Although the addition of either chloroquine or diiodohydroxyquinoline to small doses of tetracycline had little effect, a combination of the two drugs with tetracycline resulted in an immediate cure-rate of 94%. This compares favourably with the results from using tetracycline in the usual dosage, although the ulcers heal more slowly.

We should like to thank Dr. S. Disler, superintendent, King Edward VIII Hospital, Durban, for facilities.

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PSEUDOXANTHOMA ELASTICUM

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DIAGNOSIS depends primarily on the physician's high index of suspicion for certain symptom complexes; this is particularly important in the "rare" diseases, many of which are more prevalent than the sparseness of case-reports would indicate. In this paper I direct attention to the disease known as pseudoxanthoma elasticum (P.X.E.), or the Gronblad-Strandberg syndrome, in which widespread alteration in the elastic tissue produces a characteristic skin appearance, angioid streaking of the retina, and sometimes gastrointestinal bleeding which may be fatal. Every case of hæmatemesis and melæna should be examined for evidence of P.X.E. in order to avoid unnecessary surgical intervention (McKusick 1956). My first patient was recognised thus during systematic examination in the casualty department of the Manchester Royal Infirmary.

Case-reports

Case 1.—A 22-year-old, single, shorthand-typist gave a history of gradually deteriorating vision of her left eye for 6 months. She was otherwise well until 3 days before admission to hospital, when she noticed that she was passing black tarry stools. She was not taking any medicine. On the morning

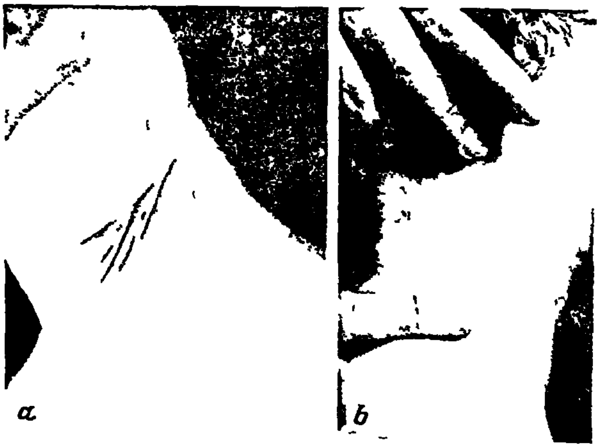

Fig. 1—Case 1: (*a*) redundant folds of skin of the neck; (*b*) coarse-grained appearance of the skin.

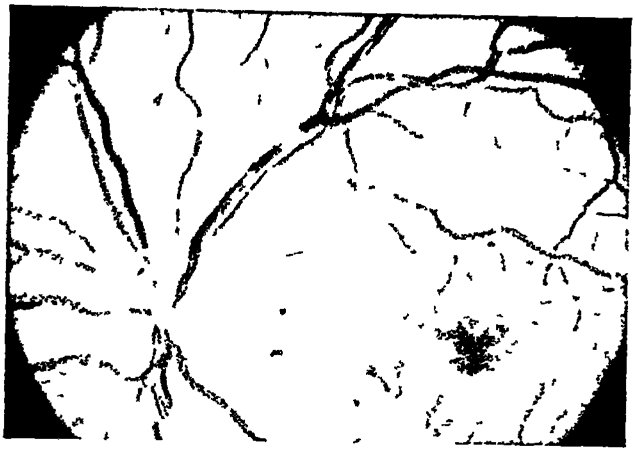

Fig 2—Case 1 Retinal photograph showing angioid streaks and pigmentation in the region of the macula

before admission she felt faint and dizzy on running upstairs, and this persisted for 5 minutes Next day (Nov 7, 1958) she rose at 5 A.M to micturate and fainted on standing upright Later in the day she felt something in her throat, and then vomited a large amount of dark red blood, containing clots She had no abdominal pain. She had not had any serious illness previously

Examination

She was slightly distressed The skin of her neck showed redundant folds and was covered with numerous yellow plaques (fig 1), some of which had apparently suppurated recently The skin of the axillæ, antecubital fossæ, and groins was affected similarly, otherwise the limbs were normal Her mucosæ were pale, there were no buccal lesions Both optic fundi showed numerous angioid streaks, and the left macula was pigmented (see fig 2) Visual acuity was J20 in the left eye and J1 in the right eye (uncorrected) The cardiovascular system was normal except for absence of the posterior tibial pulses

On admission her blood-pressure was 130/80 mm Hg, and her pulse-rate 120 per minute and regular The respiratory system and abdomen were normal The fingers were not clubbed, and there were no spider nævi Rectal examination was normal apart from melæna

Gastrointestinal hæmorrhage due to the Grönblad-Strandberg syndrome (P X E with angioid streaks in the retina) was diagnosed

Further Investigations

A skin-biopsy specimen from the right antecubital fossa was taken on Nov 11 The histological report was

> The epidermis and superficial quarter or fifth of the dermis shows changes in the elastic fibres, they are greatly increased in bulk, with bulbous or irregular swelling, and extensively fragmented Von Kossa's method shows widespread calcification of these fibres An occasional "foreign-body" giant-cell is seen alongside altered elastic fibres, but there is no other cellular reaction The collagen fibres appear more or less normal, there is perhaps a little focal formation of slender new fibres The picture is that of P X.E (figs 3a and b)

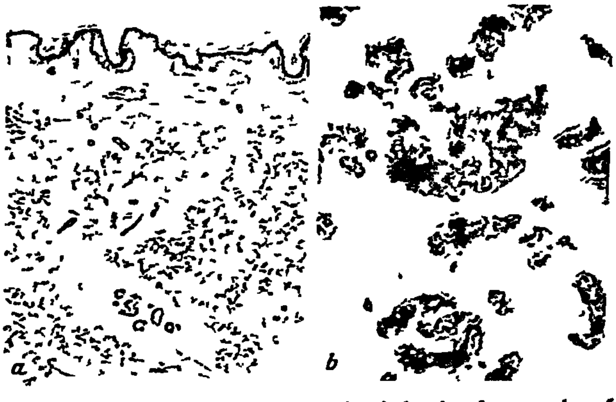

Fig 3—Skin-biopsy specimen of case 1 (*a*) showing degeneration of elastic fibres (Verhoff-Van Gieson stain for elastic tissue ×30), (*b*) showing calcification of the elastic tissue (Von Kossa's reaction for calcium ×225)

An electrocardiogram and a chest radiograph were normal Radiographs of the lower limbs showed no calcification in muscles or vessels At barium-meal examination the outline and mucosal patterns of the œsophagus, stomach, and duodenum were normal, and there was no evidence of peptic ulceration.

A full blood-count on Nov 11 showed Hb 48% (7 2 g per 100 ml), colour-index 1 0, white-cell count 8100 per c.mm. (polymorphonuclears 69 5%, lymphocytes 27%, monocytes 2%, and eosinophils 1 5%), platelets 360,000 per c mm , and erythrocyte-sedimentation rate (Wintrobe) 10 mm in the 1st hour Tests for occult blood in the fæces were strongly positive Prothrombin activity was 100%

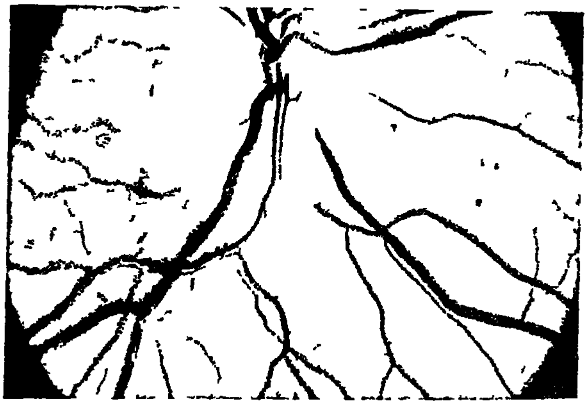

Fig 4—Case 2 Retinal photograph showing numerous angioid streaks

Liver-function tests showed serum-albumin 3 4 g per 100 ml , globulin 2 6 g per 100 ml , bilirubin 0 8 mg per 100 ml , thymol-turbidity 0 8 unit, alkaline phosphatase 6 5 King-Armstrong units, serum-glutamic-oxaloacetic-transaminase 7 units per ml , serum-protein electrophoresis normal, serum-free-cholesterol 45 mg per 100 ml , ester-cholesterol 140 mg per 100 ml , and phospholipids 200 mg per 100 ml The total fatty acids were 290 mg per 100 ml , neutral-far content was 55 mg per 100 ml , serum-calcium 10 mg per 100 ml , and serum-inorganic-phosphorus 2 9 mg per 100 ml

Progress

The hæmoglobin (Hb) on admission was 56% (8 g per 100 ml) She was given a transfusion of 2 pints of whole blood, but next day her Hb had fallen to 38% (5 6 g per 100 ml), and she was given a further 10 pints of blood over the next 5 days, while she continued to pass melæna stools The melæna abated by Nov 12, when her Hb had risen to 76% (11 4 g per 100 ml) Her blood-group was O (rhesus-positive) She was treated at first by a modified Meulengracht regimen She was discharged symptom-free on Dec 12, and has remained well When last seen on Jan 14, 1959, her Hb was 92% (13 6 g per 100 ml)

Family history

All members of the patient's immediate family were examined. Both parents were healthy, with no skin or retinal abnormality and no history of gastrointestinal bleeding or peptic ulceration. A brother, aged 18, was unaffected, but a sister, aged 14, had both skin and retinal manifestations of the Grönblad-Strandberg syndrome (case 2)

Case 2 —This girl had no symptoms Her skin showed the typical changes of P.X E She was normotensive The retinal appearances were similar to those of her sister—namely, angioid streaks and perimacular pigmentation (fig 4) She had never had gastrointestinal bleeding Skin biopsy was not performed, nor, unfortunately, was visual acuity determined

Discussion

The skin manifestations of P.X.E were first described in 1884 by Balzer, who classified the disease as one of the xanthomatoses This was corrected by Darier (1896), who named the syndrome pseudoxanthoma elasticum, and defined the histological changes in the skin The symptom-complex of skin and retinal changes associated with gastro-intestinal hæmorrhage, failing vision, and weak peripheral pulses in the same patient, was gradually unfolded in several papers over the course of 14 years, starting with Chauffard's description in 1889, followed by Besnier and Doyon (1891), Darier (1896), and finally Hallopeau and Lafitte (1903) The connection between skin and retinal changes was first clearly indicated in the classical papers of Grönblad (1929) and Strandberg (1929), because of which the disease enjoys the eponymous title of the Grönblad-Strandberg syndrome.

Clinical Features

The clinical manifestations of the disease are all dependent on the widespread degeneration of elastic fibres Collagen itself is not affected directly (Moran and Lansing 1958) The two most striking features are the changes in the skin and retina, but there are less constant manifestations—namely, gastrointestinal hæmorrhage, intermittent claudication, weakness or absence of peripheral pulses by the third decade, dilatation of the aorta, and mental changes

Skin changes may not appear before the second decade, although in the two cases here reported and in two sisters described by Worringer and Gerhard (1957) the skin changes were noticed in the first decade The sites of abnormal skin are the neck, axillæ, antecubital areas, inguinal folds, and periumbilical region The affected skin is coarser and thicker than normal, looking rather like coarse-grained Moroccan leather or a plucked chicken (Szymanski and Caro 1955), the elevations being slightly yellow The skin is often prone to pyogenic infections, elasticity is lost, and it hangs in redundant folds, particularly in the axillary and inguinal regions Buccal, rectal, and vaginal changes have been described (Giesen 1936, Carlborg 1944) But the skin may appear normal to the naked eye although histologically abnormal

Eye changes —The typical change is angioid streaking of the optic fundus, although this is not always the only finding Angioid streaks are lines fanning out from the optic disc, which vary in colour from grey to red-brown. They may be due to degeneration of elastic fibres causing cracking of Bruch's membrane, or, as Scholz (1941) suggested, to pigmentation in affected vessels Angioid streaks may occur also in Paget's disease (Scholz 1941) Other retinal manifestations are macular or perimacular hæmorrhages, colloid bodies (white or yellow discs), and central choroidoretinitis Blindness may ultimately occur

Gastrointestinal bleeding —Massive gastrointestinal hæmorrhage is common (Kaplan and Hartman 1954), and may occasionally be fatal McKusick (1956) thinks this complication is so important that in all cases of gastrointestinal hæmorrhage the physician should make a special search for skin changes Some patients have numerous hæmatemeses before the diagnosis of P.X.E. is established finally Occasionally the diagnosis is only made on histological examination of the stomach after gastrectomy (Edwards 1958) Often the entire mucosal surface of the stomach oozes blood, there being no discrete bleeding point suitable for surgical attack. Histologically there are often numerous microaneurysms, due to elastic-tissue degeneration in the gastric arteries, with intimal obliterative sclerosis Four cases of P.X.E with gastrointestinal hæmorrhage during pregnancy have been described, one of which underwent partial gastrectomy (McCaughay et al 1956, Woo and Chandler 1958) In view of the increase during pregnancy of factors which relax tissue (Allen et al. 1939), one might speculate that the mechanism of bleeding is a summation of the effect of pregnancy and damage to elastic tissue in the gastrointestinal arteries Medical treatment seems desirable for patients with P.X.E and gastrointestinal hæmorrhage rather than surgical exploration, with the almost inevitable sequel of partial gastrectomy, which can be of little benefit when the entire mucosal surface of the stomach is oozing blood. Symptoms of peptic ulceration are unusual Barium-meal examination rarely demonstrates an ulcer crater (Van Embden Andres 1952) Hæmorrhages from nose, uterus, and bladder, and into the subarachnoid space have been reported; also spontaneous hæmarthroses and purpura, without disturbance of the clotting factors The peripheral arteries may become calcified due to premature arteriosclerotic changes brought about indirectly by the damaged elastic tissue This may cause intermittent claudication, with absent or diminished peripheral pulses and peripheral arterial calcification demonstrable radiographically in the legs (McKusick 1956) The arterial degeneration may cause hypertension, intracranial aneurysm, coronary sclerosis with angina pectoris, or aortic aneurysm

Prognosis

The life prognosis in P.X.E is good, although patients may die from torrential gastrointestinal bleeding, or from premature coronary atheroma or hypertension. Blindness is common and is often the reason medical advice is sought. The occular complications cannot be treated effectively

Genetics

P.X.E is rare in successive generations but multiple involvement in individual sibships is high, indicating that the mode of inheritance is probably recessive. This should give a ratio of affected/unaffected siblings of 1/3, instead of 1/1 as in most reported cases, but this discrepancy may be due to faulty sampling Remarkably few detailed kinships of P.X.E. have been described, thus precluding adequate statistical investigation of the genetics of the disease.

Touraine (1940a and b, 1941) found that more females than males were affected, of a hundred and sixty-five cases a hundred and four were female. Cockayne (1933) suggested that P.X.E. was partly sex-limited to the female. McKusick (1959) thinks transmission is by an autosomal recessive gene, but he fails to explain the greater prevalence in females. Hermann (1956) concluded that the P.X.E. gene is usually dominant, but admitted that it may occasionally be recessive Until more case-reports with adequate family histories are published these statements cannot be subjected to adequate statistical analysis

Summary

Pseudoxanthoma elasticum (Grönblad-Strandberg syndrome) is described in two sisters

The clinical manifestations are (1) characteristic coarsening and elasticity of the skin due to widespread degeneration of elastic fibres, (2) angioid streaking of the retina causing visual deterioration, and sometimes (3) gastrointestinal bleeding, which can be fatal.

Genetically the syndrome is probably due to a recessive gene.

In management active but conservative treatment of gastrointestinal bleeding is important

My thanks are due to Dr H T Howat for permission to publish these cases, and for many valuable suggestions, to Prof D A K Black for constructive criticism, and to Sir Robert Platt for encouragement and discussion, particularly of the genetic aspects I am indebted to Prof A C P Campbell for the biopsy report and the photomicrographs, to Dr R G W Ollerenshaw of the department of medical illustration for the clinical photographs, and to Dr P J D Snow for the retinal photographs

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SALMONELLA OSTEITIS IN NIGERIAN CHILDREN

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SALMONELLA osteitis is a rare clinical entity, by 1950 only nineteen cases had been recorded (Wigh and Thompson 1950) Patients with sickle-cell anæmia, however, seem to be peculiarly susceptible to this complication Hodges and Holt (1951) first drew attention to the relation between sickle-cell anæmia and salmonella infections, though isolated examples had been reported as early as 1937 (Diggs et al 1937)

Vandepitte et al (1953) described five cases of salmonella osteitis seen in patients with sickle-cell anæmia in the Belgian Congo, and mentioned the association Earlier a greater susceptibility to salmonella infections had been observed among sicklers than non-sicklers in the Belgian Congo (Lambotte-Legrand and Lambotte-Legrand 1951) In 1957 Hook et al were able to find twenty-nine reported instances, and to add four new cases of their own In 1958 Roberts and Hilberg described four more cases of salmonella osteitis complicating sickle-cell disease, one of their patients having sickle-cell hæmoglobin-C disease It has become increasingly apparent that the occurrence of salmonella osteitis and sickle cell anæmia is not merely fortuitous The *British Medical Journal* (1957) stated " It seems therefore established that there is a highly significant association between salmonella osteitis and sickling," and drew attention to the possibility, suggested by the Lambotte-Legrands (1951) and Raper (1956), that carriers of the sickle-cell trait might be more liable to salmonella infections than non-sicklers, which would call for reorientation of " our conceptions of the population dynamics of sickling "

TABLE I—SALMONELLA OSTEITIS IN PATIENTS WITH SICKLE-CELL ANÆMIA

Case no	Age (yr)	Sex	Site	Bacteriology
1	9	M	Both ulnæ, left radius, both tibiæ	Salmonella isolated from blood, serum agglutinated *S dublin* (g p) 1/1280 and *S typhi* O (9, 12) 1/320
2	1¼	F	Multiple phalanges, metacarpals, metatarsals, and left radius	Salmonella belonging to group B isolated from pus and stools
3	3	M	Both femora	Salmonella isolated from blood, serum agglutinated *S typhimurium* H (i) 1/1280
4	¾	M	Left radius, multiple phalanges of feet	Serum agglutinated *S typhi* O (9, 12) 1/640, *S enteritidis* H (g.m) 1/1280, and *S menston* H (g s t) 1/640
5	1	F	Bilateral metatarsals	*S dublin* isolated from pus
6	3¼	M	Bilateral radii, ulnæ, and tibiæ	Serum agglutinated *S paratyphi C* O (6, 7) 1/320, and *S paratyphi* C H (c) 1/1280
7	1¼	F	Bilateral metatarsals and right ring finger	*S dublin* isolated from pus, serum agglutinated *S dublin* H (g p) 1/1280, *S menston* H (g s t.) 1/640, and *S london* O (3, 10) 1/160

The object of this paper is to report thirteen cases of salmonella osteitis seen in the children's department of University College Hospital, Ibadan, between June, 1956, and October, 1958 In seven instances infection was in a proved case of sickle-cell anæmia One patient was a non-sickler In the other five patients sickling tests were not performed One of this group was an 8-day-old infant, and, in view of the known paucity of sickled cells in the blood of the newborn (Watson et al 1948), it seems highly unlikely that sickling per se was related significantly to the infection

Clinical Findings

SALMONELLA OSTEITIS IN SICKLE-CELL ANÆMIA

Table I shows the age, sex, sites involved, and bacteriology in seven cases of sickle-cell anæmia complicated by salmonella osteitis All recovered on chloramphenicol, but in the majority the response was slow, and treatment had to be continued for long periods

Illustrative Case-report (*Case 7*)

A Yoruba girl, aged 15 months, presented with painful swelling of the hands and feet of 4 days' duration, associated

TABLE II—SALMONELLA OSTEITIS IN FIVE PATIENTS WHOSE HÆMOGLOBIN GENOTYPES WERE NOT KNOWN, AND IN ONE NON-SICKLER

Case no	Age	Sex	Site	Bacteriology	Comment
8	3 mos	F	Left humerus and left scapula	*S enteritidis* isolated from stools and pus	Anæmia, hepatosplenomegaly, terminal bronchopneumonia, died
9	1 yr	F	Right femur (lateral condyle)	*S enteritidis* isolated from pus	Hæmoglobin 60%, general condition good, no hepatosplenomegaly, good recovery
10	8 days	F	? Left femur	*S enteritidis* isolated from blood	Toxic deeply jaundiced premature infant, died within 12 hours of admission
11	9 mos	F	Right scapula	*S chailey* isolated from pus	Not anæmic, good recovery
12	5½ yr	F	Both tibiæ	*S ank* (' new species') isolated from pus	
13	14 mos	F	Right knee, left humerus	*S saint paul* isolated from pus from both sites	Non-sickler, hæmoglobin 38%, presented with diarrhœa, dehydration, and bronchopneumonia, osteitis apparent 11 days after admission, good recovery

with fever She was pyrexial and anæmic. There were tender brawny swellings over the dorsum of both feet, and a tender fluctuant swelling over the proximal phalanx of the right ring finger The liver was palpable. No other abnormality was found clinically

Special investigations—Hæmoglobin 6 1 g per 100 ml.; white blood-cell count 18,800, sickling positive, hæmoglobin electrophoresis showed hæmoglobin S only Pus aspirated from the ring finger grew *Salmonella dublin* on culture. The serum agglutinated the following

S dublin H (g p) at 1/1280
S [illegible] H (g.s.t.) at 1/640
S london O (3, 10) at 1/160

Radiographs taken when the patient first attended showed changes attributable to sickle-cell anæmia only, but later films showed osteitis of several metatarsals and the proximal phalanx of the right ring finger

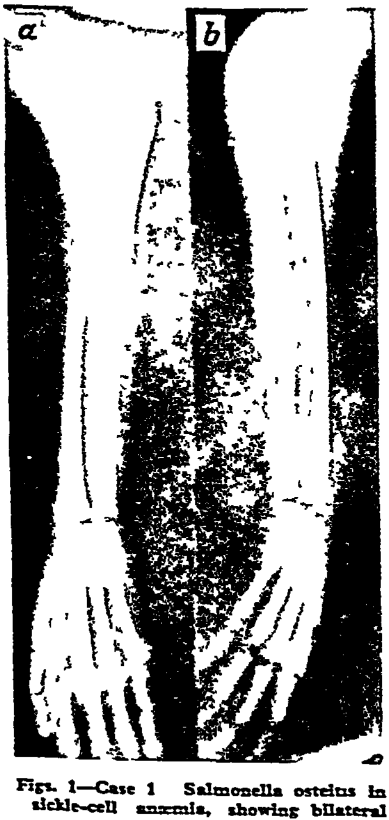
Progress—The child was treated with chloramphenicol, and the osteitis resolved completely

SALMONELLA OSTEITIS IN PATIENTS WITH UNKNOWN HÆMOGLOBIN GENOTYPES, AND IN A NON-SICKLER

Table II shows the age, sex, site, salient clinical features, and bacteriology in five cases of salmonella osteitis in which the hæmoglobin genotypes were not known, and in one patient who was a non-sickler All were treated with chloramphenicol except case 11, which appeared to respond to chlortetracycline.

Discussion

These thirteen cases represent the largest series of salmonella osteitis described to date. Unfortunately, information about erythrocyte sickling is not available in five Taking into account the many cases of sickle-cell anæmia in the Ibadan area (25% of the population show the sickle-cell trait [Garlick and Barnicot 1957]), some of these are likely to have been cases of sickle-cell anæmia. The clinical findings in one instance (case 8) were highly suggestive of the disease. Our finding seven examples of salmonella osteitis in proven cases of sickle-cell anæmia supports the observation that people with sickle-cell anæmia are peculiarly susceptible to this complication There can be little doubt that the association is significant.



Figs. 1—Case 1 Salmonella osteitis in sickle-cell anæmia, showing bilateral symmetrical involvement of ulnæ.

Ten of our thirteen cases were seen during the months of July to November Conclusions about the seasonal incidence of salmonella osteitis cannot be drawn from so small a series, but analysis of the monthly isolations of salmonellæ in Ibadan during 1956 showed a definite peak incidence during the months of June, July, and August (Collard and Sen 1958), when the rainy season is at its height. The observed incidence of osteitis in our cases correlates with Collard and Sen's findings if we allow a time-lag between bowel infection and the onset of osteitis In five cases we obtained a clear history of diarrhœa preceding the osteitis, and in two, identical strains of salmonellæ were isolated from pus and stools

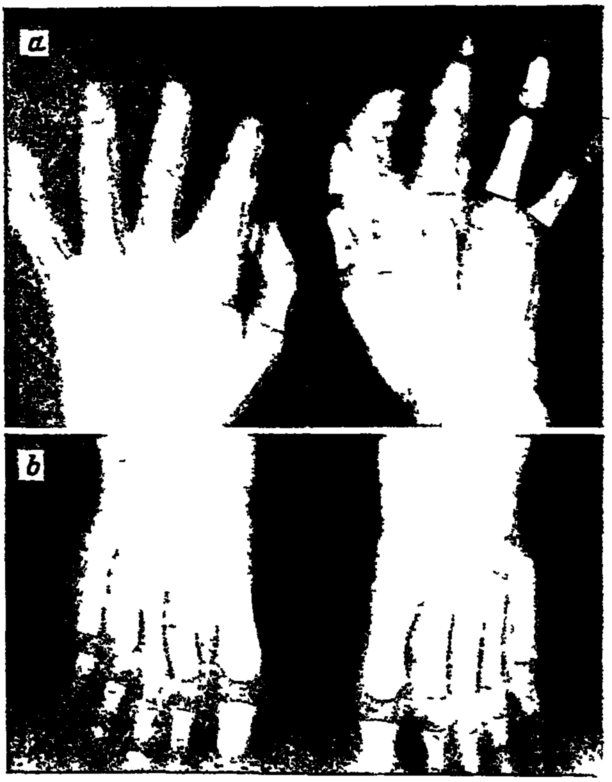


Fig 2—Case 2. Salmonella osteitis in sickle-cell anæmia involving many bones in hands and feet. Note the symmetrical involvement of the index figures and fifth metatarsals.

In our series salmonella osteitis was most frequent in the first 2 years of life, nine of our thirteen cases fall into this age-group Other reports also show a higher incidence in this age-group than at any other time (see Hook et al. 1957, Roberts and Hilberg 1958) This finding is probably determined by

(1) The high incidence of gastrointestinal infections during infancy, especially in underdeveloped areas.

(2) The progressive fall in the number of patients with sickle-cell anæmia seen in successive age-groups. This results mainly from increase in mortality but the observed tendency for the disease to become attenuated with age may be a contributory factor (Lambotte-Legrand and Lambotte-Legrand 1951, 1955, Trowell et al. 1957, Scott et al. 1955, Hendrickse 1959)

Until 1957 reports indicated that males were more often affected than females (3/1), and that *S paratyphi B* or *S typhimurium* accounted for 67% of infections (Hook et al. 1957) Our own findings differ Nine cases were female and four were male, and eight different species of salmonellæ were isolated. The only organism frequently encountered was *S enteritidis*, which was found in four cases The majority of the eight types isolated belonged to serotypes associated with an invasive clinical picture.

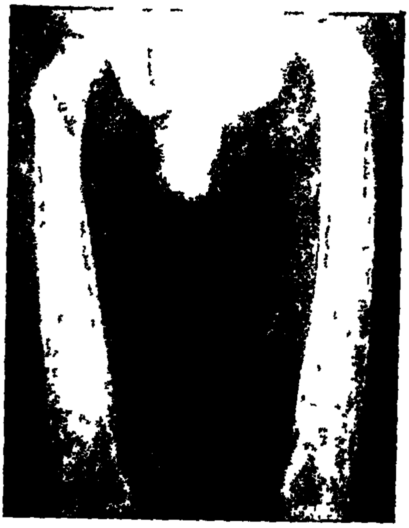


Fig 3—Case 3 Salmonella osteitis in sickle-cell anæmia, with bilateral symmetrical involvement of femora

Sickle-cell anæmia often masquerades as osteitis These patients are prone to episodes of fever, accompanied by pain and sometimes swelling over bone, associated with leucocytosis and sometimes radiological changes in bone due to infarction Clinically these episodes are virtually indistinguishable from acute osteomyelitis except by their course and response to treatment When osteomyelitis does arise, the clinical picture varies very little with different pathogens, except in the response to treatment In general, salmonella osteitis responds only to chloramphenicol, but even with optimum dosages of this drug response is slow, and relapses tend to follow months or even years after apparent eradication of infection (Hook et al 1957)

Table I and figs 1–3 show that multiple sites were affected in all our cases, and that in some the lesions were bilateral and symmetrical This agrees with other reports (Smith 1953, Vandepitte et al 1953, Hook et al 1957, Hughes and Carrol 1957, Wigh and Thompson 1950, Goldenberg 1955) Such a distribution of osteitis is not peculiar to salmonella infections but is seen with other organisms as well Further, the sites most often affected by osteitis are similar to those most often involved in the spontaneous peripheral manifestations of sickle-cell anæmia The obvious inference is that areas devitalised by the pathological processes peculiar to the disease become infected by a transient bacteræmia, which in normal persons usually has no serious consequences Two other factors probably also contribute to the high incidence of salmonella osteitis in sickle-cell anæmia

(1) Capillary thrombosis consequent on intravascular sickling, which probably decreases the resistance of the gastrointestinal tract to invasion by pathogens, and (2) salmonellæ may remain dormant in bone-marrow for long periods (Vandepitte et al 1953, Roberts and Hilberg 1958)

Normal people harbouring the organism usually remain symptom-free, though occasionally localised circumscribed areas of osteitis (Brodie's abscess) may arise In sickle-cell anæmia debility lowers the general resistance to infection, and thrombotic episodes in hæmopoietic tissue and bones lowers local resistance In these circumstances active infection is to be expected sooner or later in anyone harbouring the organism

Autosplenectomy in sickle-cell anæmia has been suggested as an additional factor in lowering resistance to infection and predisposing to invasion by salmonellæ (Hook et al 1957) While the theoretical grounds for this suggestion cannot be contested, most cases of salmonella osteitis reported are of an age where autosplenectomy is rare Among more than two hundred cases of sickle-cell anæmia under 10 years of age seen in the children's department at University College Hospital, Ibadan, more than 70% had splenomegaly, and autosplenectomy was not observed Thus in our series autosplenectomy does not seem to be a significant factor in determining salmonella osteitis in sickle-cell anæmia

Summary

Thirteen cases of salmonella osteitis in Nigerian children are reported In seven cases salmonella infection complicated sickle-cell anæmia, in five erythrocyte sickling was not looked for, and one patient was a non-sickler

Our findings suggest a seasonal incidence, and indicate that salmonella osteitis is commonest during the first 2 years of life Eight strains of salmonellæ were isolated *Salmonella enteritidis* was found in four cases

The peculiar susceptibility to salmonella osteitis of persons with sickle-cell anæmia may be due to (1) diminished resistance of the gastrointestinal tract to invasion by pathogens, and (2) diminished resistance to infection in the hæmopoietic tissue and bones These both result from tissue ischæmia following intrascular sickling and thrombosis Autosplenectomy is unlikely to have any great significance in determining the incidence

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INDUCTION OF ANÆSTHESIA IN YOUNG CHILDREN*

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Many studies of the psychotraumatic aspects of pædiatric surgery and anæsthesia have shown that not all young children survive a stay in hospital unscathed (Gwathmey 1936, Coleman 1950, Albany Research Project 1952, Eckenhoff 1953, Levy 1955, Junkin 1956) The possible causes of psychic trauma (nursing, anæsthesia, surgery, maternal separation) are not segregated easily, though some reports dissociate unjustifiably the induction of anæsthesia from the general adverse effects Failure to provide suitable sedative premedication is often regarded as a major ætiological factor in late psychic upsets (Slater and Stephen 1951) Unfortunately, therefore, efforts have been directed primarily towards improving premedicant drugs (Slater and Stephen 1951, Rendell 1954, Gusterson 1955, 1957) rather than towards lessening the general psychic trauma of surgery and anæsthesia Incidentally premedication itself may lead to psychic trauma (Barnes 1952, Ellison 1955, Goulding et al 1957, Halstead 1955, Rollason 1955, Morton 1957)

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* Being part of a paper gaining a research prize awarded by the South West Metropolitan Regional Hospital Board, 1958

In most children subjected to "everyday" surgical procedures adequate sedative premedication is either contraindicated or impossible Of nearly nine thousand such children anæsthetised in 1957 in one hospital group, 90% were outpatients or underwent otolaryngeal procedures (Hodges 1959) I believe that failure lies not in lack of premedication but in the way the children are approached and in their reactions to an unpleasant anæsthetic experience

In a large series of unpremedicated or lightly premedicated children I gained the impression that an anæsthetic technique based on either a single dose of thiopentone, or on thiopentone and nitrous-oxide/oxygen (with suxamethonium where necessary in the longer procedures) lessened some of the untoward sequelæ associated with induction and recovery from the anæsthetic

Psychiatrists strongly support the belief that neither docile resignation nor an outward calm in the face of disturbing circumstances indicates reliably a child's emotional state Hence I thought that further study of the true emotional state was necessary before the technique of inducing anæsthesia intravenously in children with little or no premedication is accepted as successful

The Patients

Children having their tonsils and adenoids out (the most common operation in elective pædiatric surgery) are ideal for studying the psychic trauma of introduction to hospital In otolaryngeal surgery many think that sedative premedication is contraindicated These patients, therefore, fulfil the criteria for "everyday" anæsthesia Their basic reactions to environment and experiences, unmasked by drug sedation, can be studied, providing a baseline for the assessment of premedicant drugs

A hundred and fifty-five children admitted consecutively for adenotonsillectomy were studied They were aged from 3 to 12 years, but they mostly fell into the 4½–7½ age-groups (fig 1)

Children with whom one cannot establish contact (usually, though not invariably, the under-3-year age-group) constitute a special problem. Therefore those who could not be approached verbally because of age (three patients), language difficulties (three patients), or congenital maldevelopment (four patients), were excluded from the series Three children over the age of 10½ years were excluded also because in this more mature group the problems are less Thus a hundred and forty-two children remained in the series

Method

Admission

24 hours before surgery, the children were admitted to an ear, nose, and throat surgical ward catering exclusively for them. Children in various stages of their hospital stay were intermingled, and, as far as their surgical condition allowed, encouraged to play together They were screened from the rest of the ward immediately before and after operation, and no new patients were admitted meanwhile. The short-stay routine surgical patients were not visited by their parents

Preoperative Approach

My practice is to visit these children on the morning of admission. The necessity for a "psychological approach" to children has been stressed often (*British Medical Journal* 1954, Leigh 1949, Collins and Granatelli 1956), and the advantages of intelligent cooperation are obvious

The technique is not, as many think, time-consuming. These children were treated satisfactorily as a group, and not more than 20 minutes was spent in the essential preoperative examination and explanation. I hold what I call a "pre-anæsthetic class" for the ten to fifteen children scheduled for operation next day, and I think the children find it encouraging to be together The interviews are informal but disciplined.

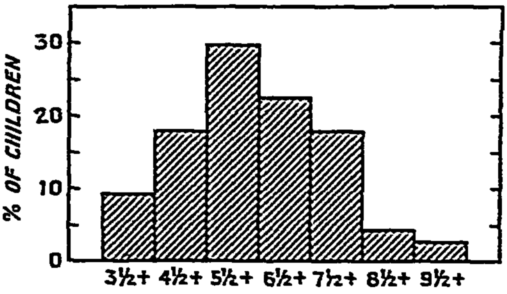

Fig 1—Age-distribution of the children studied.

The children are asked whether they understand why they are in hospital, and then the preoperative ritual is explained, and, if necessary, demonstrated simply Questions are encouraged and answered No promises of freedom from pain or discomfort are made Once explained, the procedure should be followed implicitly, for it is the unexpected that alarms most. The importance of a truthful explanation cannot be stressed too highly Most reasonable parents appreciate this, but through their own ignorance they may be unable to explain adequately

Premedication was by atropine gr 1/100 (0·6 mg) by hypodermic injection in the early part of the investigation, and by mouth in the later part.

Before operation the children were segregated in a side-room and then taken in turn to the nearby operating-theatre by the theatre porter Unnecessary people were kept out of the anæsthetic room, and face-masks were not worn.

Induction of Anæsthesia

Thiopentone sodium intravenously was used to induce anæsthesia in all cases but one (case 30) This technique has a particular advantage

If a child's resolution breaks down during induction he can be calmed and reassured after venepuncture and before injecting thiopentone In my experience, this has rarely been possible with a child who has become distressed in the initial stages of an inhalation induction.

During the induction of anæsthesia two observers attempted to classify the apprehensiveness of the patient into five grades Grades 1 and 2 were regarded as successful inductions, grades 4 and 5 as unsuccessful, and grade 3 as intermediate Variations were recorded in these grades between the time the child entered the anæsthetic room and the establishment of anæsthesia.

Maintenance of Anæsthesia

Anæsthesia for tonsil dissections was maintained with thiopentone intravenously followed by 60–70% nitrous oxide in oxygen through an endotracheal tube, which was passed nasally after suxamethonium had been given intravenously Small increments of the relaxant were repeated as necessary No other inhalation agent was used. When the tonsils were guillotined a single dose only of thiopentone was used (Hodges 1955)

After Operation

I make a point of talking with each child as soon as possible after consciousness is regained, and at least once before discharge from hospital, particularly if he has been upset by his experience Much can be done by way of reassurance at this stage to make future encounters smooth.

The children were given a sedative after operation when necessary (usually an opiate derivative in small doses), and they were kept in bed for 24 hours They stayed in hospital for about 4 days, depending on the type of operation. The ward-sister was asked to make notes of any abnormal behaviour

Follow-up

A month after operation I saw the children as outpatients A questionnaire was sent to the parents of each child after 2–3 months and again after 2½ years With each questionnaire a covering explanatory letter was sent stating the object and

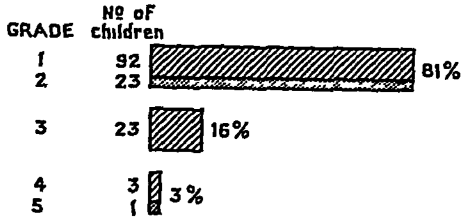

Fig 2—Grading of apprehension at the time of venepuncture

aims of the investigation Finally the results of the first questionnaire were compared with those in a similar series of children who had had anæsthesia induced by inhalation, but who were treated comparably otherwise

Results

Technique

In three of the hundred and forty-two children venepuncture was difficult, and in one (case 30) it was abandoned No local complications arose from the intravenous injections

Apprehension

The gradings at the time of venepuncture represent the greatest apprehension of the children during the period in the anæsthetic room (fig 2) Though many were successfully upgraded, no child became more apprehensive afterwards (fig 3) Only three times was a child precipitated from grade 1 to grade 3 by intravenous injection, and then not irretrievably

These results correspond closely to the clinical impressions gained in many years' study of induction of anæsthesia intravenously

In the initial clinical assessment of the whole series (table I), there is a suggestion that the younger children are more susceptible to psychic trauma as judged by their reactions during anæsthetic induction 6% of children under $5^1/_2$ years, compared with 2% of children over this age, had an unsuccessful induction

Postoperative Course

Immediately after recovery of consciousness I found the children neither difficult to manage nor resentful No child was persistently distressed, and no abnormality nor behaviour change was obvious in hospital This impression was confirmed in outpatients later Only two children were obviously reluctant to return to hospital, one had been told by his parents when brought for admission that " he was NOT going to stay in ", and the other, a 4-year-old, was very dependent on his mother

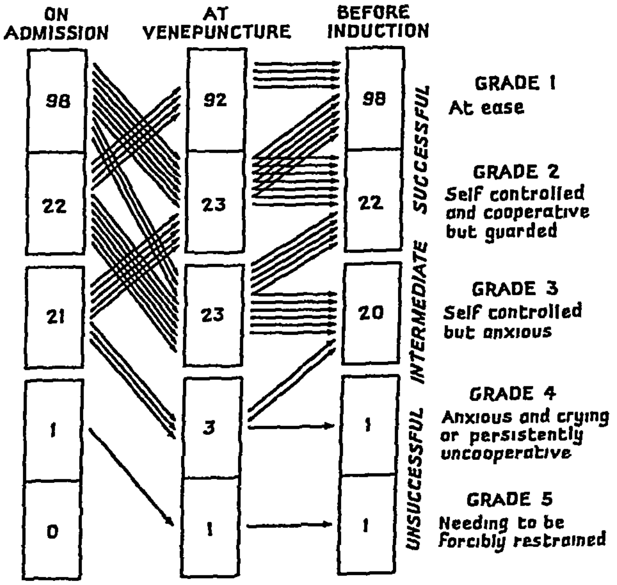
ON ADMISSION
AT VENEPUNCTURE
BEFORE INDUCTION
98
22
21
1
0
92
23
23
3
1
98
22
20
1
1
SUCCESSFUL
INTERMEDIATE
UNSUCCESSFUL
GRADE 1
At ease
GRADE 2
Self controlled and cooperative but guarded
GRADE 3
Self controlled but anxious
GRADE 4
Anxious and crying or persistently uncooperative
GRADE 5
Needing to be forcibly restrained

Fig 3—Grades of apprehension at 3 stages in the anæsthetic room (The arrows indicate changes)

Answers to Questionnaires

Detailed replies to the first questionnaire were received from the parents of a hundred and nineteen children—i e , 84% of the parents circularised There seemed to be a higher proportion of replies from the group classified clinically as intermediate and failures, than from the more successful cases, but in all other respects there was no difference between the children of those parents who responded to the questionnaire and those who did not

The replies to the questions are outlined in fig 4*a* analysed below

Previous hospital experience—Nineteen children had had some previous experience of hospital, but, according to the parents, only six (5%) were old enough at the time to appreciate it Five children had previously had an anæsthetic—all as outpatients—and one of them (case 60) had had two

TABLE I—CLINICAL ASSESSMENT OF 142 CHILDREN RELATING AGE TO STATE OF APPREHENSION

Age-group (yr)	$3^1/_2$	$4^1/_2$	$5^1/_2$	$6^1/_2$	$7^1/_2$	$8^1/_2$	$9^1/_2$	Total
Total no of children	9	24	38	36	20	13	2	142
No in each grade								
Grade 1	4	14	23	27	13	9	2	92
" 2	4	4	6	5	2	2		23
" 3	1	4	9	4	3	2		23
" 4		1			2			3
" 5		1						1
No with failed (group 4–5) inductions	0	2 (*8%*)	0	0	2 (*10%*)	0	0	4 (*3%*)
	6%		*2%*					

Reasons given for hospital admission —The reasons supplied by the parents to their children were classified as adequate, when a simple truthful explanation had been given, or inadequate, when the explanation might have led the child to expect something different from what was to happen Explanations based on the necessity to cure some chronic symptom of which the child was quite aware, but without details of what would happen, were also considered adequate—e g , " to cure those coughs and earache " Obviously inadequate explanations included such fantasies as " like going to fairyland ", or " like a holiday from school ", and such deliberate deceptions as " the doctors are only going to look ", or " you're not going to stay in " Explanations were also classified as inadequate when the treatment was allegedly to improve some vague condition in which the child had no interest or of which he might be unaware—e g , " to stop you snoring ", or " because your tonsils are too big " Sometimes it was impossible to decide whether or not the explanation offered was adequate, but nine children (8%) had been given an obviously inadequate explanation

What did your child think of his or her stay in hospital?—The parents of 75% of the children said that their child was contented and happy in hospital Many children were enthusiastic, often using expressions such as " I enjoyed it " (forty-nine children), " I wish I could have stayed " (four children), or " it was very nice " 18% of the children expressed no adverse comment but had no particular liking for their experiences Only 7% commented adversely Two children were " not keen "—one because of homesickness Two were " disappointed " Two were " rather unhappy "—one because of fear of smells and injections (case 30) and one because of homesickness Two children who gave an unqualified " did not like it " were a 9-year-old delinquent boy and a wayward 8-year-old girl

Comparison with previous experiences —In the few cases where this question applied no significant information was gathered

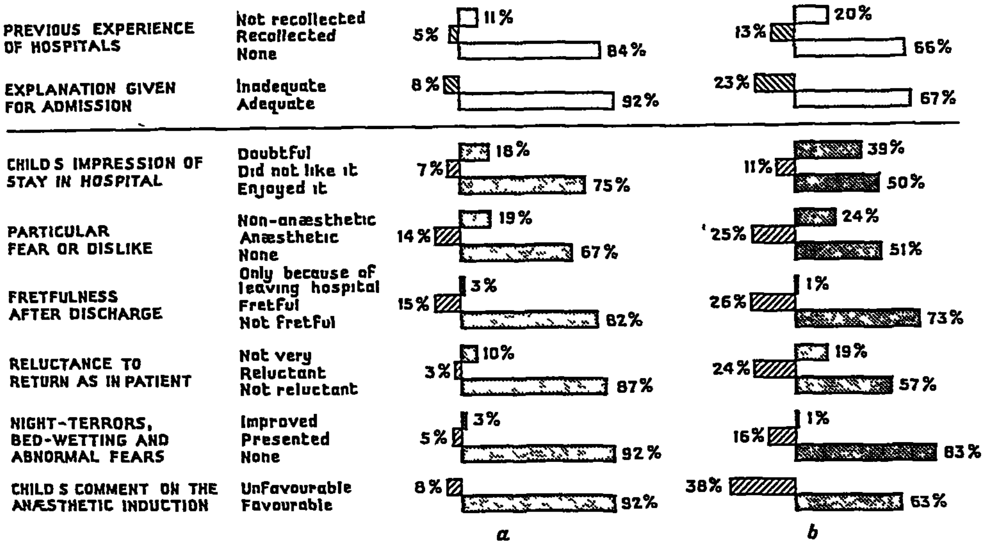

Fig 4—Replies to the questionnaires (*a*) anæsthesia induced intravenously, (*b*) anæsthesia induced by inhalation

Was there anything that the child particularly disliked or would be frightened of in the future?—Seventy-nine children (66%) had expressed no particular fear or dislike Forty children had dislikes, but in twenty-three they were not associated with the anæsthetic These dislikes were minor and insignificant (mouthwashes, food, nightclothes, toys, cots) with the exception of two children who were homesick. Nineteen children had fears which could not be dissociated from anæsthesia Two were frightened of the hospital " atmosphere ", smells, equipment, &c. In case 60 this fear was related to the previous admissions to hospital, he was consequently only reluctant to return to the previous hospital Three other children were reluctant to return to hospital, and these together with twelve others (13%) " disliked " injections, but in only one child (case 30) did this amount to fear Seven were referring to their premedication hypodermic atropine and not to the intravenous injection. (Because in the early part of the investigation several children found the atropine injection was their most unpleasant experience, the premedication was later given by mouth)

TABLE II—RESULTS OF SECOND QUESTIONNAIRE

Question	Answer	No of children
Does child talk of hospital now?	When reminded or asked	6
	Still mentions " smells "	1*
	Only to comfort others	1
	Only lightheartedly	1
	Does not want to return	1
	Never mentions it	8
Was child permanently upset?	Not permanently	2
	Not at all	16
Did behaviour change persist?	No	17
	Recent tantrums	1
Has child been to hospital since?	No	16
	Yes	2
Did child go quite willingly?	Not applicable	16
	Yes	2

* This child was anæsthetised by an inhalation technique (case 30)

Was your child fretful after leaving hospital?—Three mothers replied, in effect, " only because he didn't want to come home " Eighteen others (15%) were fretful after leaving hospital, but in only one child (case 60) was this more than slight and transient

Would your child be reluctant to become an inpatient again, and why?—The parents of a hundred and four children (87%) said " no " dogmatically Twelve (10%) said " Not very, but " Three of these children had been homesick, one was fearful of the hospital " atmosphere ", and eight showed reluctance for unspecified reasons Only three children were extremely reluctant to return Two of these were below school age and homesick, and one (case 30) was frightened of needles

Behaviour changes—A hundred and four children showed no change in behaviour and in four children previous behaviour difficulties were improved In eleven children changes of some sort appeared for the first time, or an established difficulty became worse Minor fears—e g, of smells and strangers—arose in five patients and severe night terrors in six (5%)

Did your child make any comment on how he or she was put to sleep for the operation?—A hundred and ten children (92%) made favourable or non-committal remarks—e g, " just a prick ", " it didn't hurt a bit ", " I didn't mind ", " it was wonderful ", &c. Of the five children who had previously had an anæsthetic three said that it was " better than the mask ", one (case 60) " did not like the smell " (a reply which may have been related to the previous experience), and the other said he would " rather have a balloon " The parents of nine children (8%) gave unfavourable replies, in eight cases because of the injection.

Other comments included a mixture of helpful suggestions, minor criticisms, and thanks, which were not strictly relevant to this paper

The replies to the second questionnaire were either entirely negative or were a recapitulation of the facts already known In none of the eleven patients had the previously reported behaviour change persisted The replies from the parents of these and eleven other children in whom at the final assessment there was reason to doubt the success of the technique are listed in table II)

Classification of Findings

The children can be divided into two groups In group 1 all psychic trauma had been avoided, but in group 2 it had not (see table III)

The children in group 1 showed no fretfulness nor behaviour changes after operation, and their parents thought they would submit willingly to a similar procedure Ninety-seven children (82%) fall into this category as judged by the results of the first questionnaire These included eighty-one of the ninety-five children in whom anæsthesia had been induced successfully on clinical grounds, thirteen of the twenty-one classified as intermediate, and all those classified as failures In none of the children with clinically successful inductions who ulti-

TABLE III—CLASSIFICATION OF 119 CASES FOLLOWED-UP FOR 2$^1/_2$ YEARS AFTER OPERATION

Grade of state of apprehension at induction	1 and 2	3	4 and 5	Total
Group 1 (successful) No fretfulness, no behaviour change, would be willing to submit to similar procedure again	81	13	3	97
Group 2a (successful) Same as group 1, but fretful postoperatively	8	3		11
Group 2b (unsuccessful) Children with postoperative behaviour changes				
Minor	3	2		} 11
Major	3	3		
Total	95	21	3	119

mately showed psychic trauma could anæsthesia be incriminated Thus clinical assessment seems to be a fairly reliable though possibly pessimistic guide to the success of anæsthetic induction

Most of the children (eighty-eight) in group 1 made no adverse comment on the induction of anæsthesia, but nine confessed to a dislike of "needles" Seventy-seven admitted to no dislike or fear, but eighteen had a minor dislike of some sort which was not related to the anæsthetic, and one child mentioned homesickness

The general impression gained was that, far from being harmed, most of the children in group 1 had benefited from their stay in hospital The experience was of a maturing nature The parents said, for example, "it made her feel quite grown-up, and she loved helping the nurses" or "it was an enjoyable adventure, something to boast about" Even children who appear distressed when anæsthesia is induced, and who may show reluctance to return to hospital, have probably not undergone psychic trauma provided that they show no specific fear and no behaviour changes after operation

The children in group 2 are more difficult to assess In 27% of cases (compared with 8% throughout the whole series) the parents had given inadequate explanations of the reason for admission The second questionnaire was completed by 82% of the parents of these children (table II)

TABLE IV—THE PROBABLE CAUSE OF PSYCHIC TRAUMA IN CHILDREN WITH POSTOPERATIVE BEHAVIOUR CHANGES

Case no	Age (yr & mo)	Particular dislike	Reluctance to return	Induction comment	Behaviour change	Cause of psychic trauma
68	$7^1/_{12}$	+	+	?	Fear of smells	Hospital "atmosphere"
78	6		+		Fear of strangers	Maternal separation
119	$4^1/_{12}$		+		"	"
94	$7^7/_{12}$	+ (anæsthetic)			"	Anæsthetic
147*	$4^6/_{12}$		+++		" and smells	Parental deceit
85	$7^1/_{12}$	+	+		Night terrors	Maternal separation
76	$7^1/_{12}$	+	+		"	Inadequate parental preparation
43*	$5^{10}/_{12}$				"	Maternal separation
143	4	+	+		"	"
148	$4^6/_{12}$	+ (anæsthetic)			"	Anæsthetic
11	$6^8/_{12}$	+ (anæsthetic)	+	+	"	"

* Did not reply to the second questionnaire

Within group 2 the children can be divided into two categories Those in the first category may have had some shortlived minor upset (e g, homesickness, dislike of injections, or discontent) as signified by their transient fretfulness, but, as none of these children had any other behaviour change, their management can probably be regarded as successful In the second category the children all showed behaviour changes, and their management cannot be regarded as successful The psychic trauma which caused minor behaviour changes was attributable to the anæsthetic in only one case, but in two children with major behaviour changes anæsthesia was probably responsible (table IV)

TABLE V—RELATION OF AGE TO FINAL ASSESSMENT IN CASES WHICH WERE NOT CONVINCINGLY SUCCESSFUL

Age-group (yr)	$3^1/_2$+	$4^1/_2$+	$5^1/_2$+	$6^1/_2$+	$7^1/_2$+	$8^1/_2$+	$9^1/_2$+
No in final classification							
Group 2a	1	1	3	4	2		
Group 2b	2	2	3	2	2		
Percentage of each age-group	33%	13%	16%	17%	20%	0	0
	18%		15%				

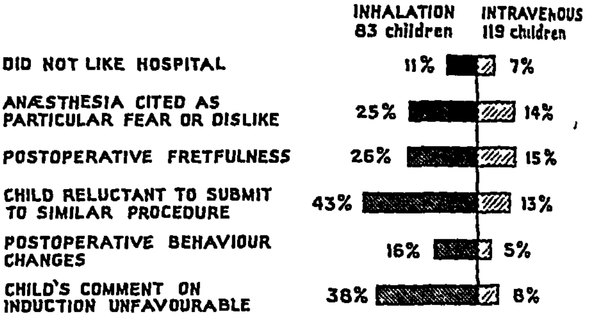

Fig 5—Comparison between sequelæ of anæsthesia induced by inhalation and by intravenous injection

Three patients (2%) in the whole series, therefore, could be regarded as showing psychic trauma due to anæsthesia At first it seemed that the younger children were more susceptible to psychic trauma (table I) But in the final assessment, taking all factors into consideration, age had less statistical significance than had been expected 18% of the children below $5^1/_2$ years and 15% of those above this age fell into group 2 (table V)

Finally, in an attempt to assess the value of intravenous induction of anæsthesia, the results of analysis of the first questionnaire were compared with those from the previous study in which the children were anæsthetised by open induction (fig 4*b*) The obvious and significant difference in the results (fig 5) is heavily in favour of those children in whom anæsthesia was induced intravenously

Conclusions

Of the hundred and forty-two children, most (84%) had not been in hospital before, but despite the anæsthetic and operation many (75%) were said to have enjoyed their stay Still more (87%) would submit, in the opinion of their parents, without protest to a similar procedure if it became necessary

The intravenous induction of anæsthesia in these children (without sedation) was technically successful in over 99% of cases, and only 3% were distressed during the induction period In only 2% could the anæsthetic be incriminated as a cause of behaviour changes

The results demonstrate clearly that psychic trauma is not an inherent part of anæsthesia and surgery, and that good results can be achieved without any drug premedication This series may be useful as a baseline for assessing premedicants given to children

In this series two factors seem to be mainly responsible for success—namely, the way the children were treated by everybody concerned and the method of inducing anæsthesia by giving thiopentone intravenously, which was neither frightening nor toxic

In children admitted to hospital factors other than anæsthesia may be more often responsible for psychic trauma Of the specific dislikes here encountered, 58% were not associated with the anæsthetic Homesickness was not uncommon among both the successful and unsuccessful cases Although it has always been accepted that the difficulties are greater in the very young, there was no significant correlation between age and success But children under 3 years should not be admitted to hospital for elective surgery if this can safely be postponed

Using this technique avoidance of psychic trauma depends not on the anæsthetist alone but on the whole team One person's lack of kindness and gentleness may utterly outweigh the highest degree of skill shown by any other

I should like to record my appreciation of the assistance and tolerance shown by my colleagues—anæsthetists and surgeons alike My thanks also go to the sisters and nurses, the theatre porters, and all concerned with the handling of these children, to the hundreds of parents who responded to the questionnaires, and to the thousands of children who directly and indirectly assisted me in this investigation

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A PERSPEX ICTEROMETER FOR NEONATES

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The icterometer is a simple device for estimating quickly the depth of jaundice in newborn babies at the cotside without taking a blood specimen The principle is to blanch the baby's skin by pressure, and match the resulting shade of yellow against a colour scale

The device is valuable as a means of (1) following the depth of jaundice in individual babies from day to day, and (2) indicating which babies ought to have their serum-bilirubin estimated

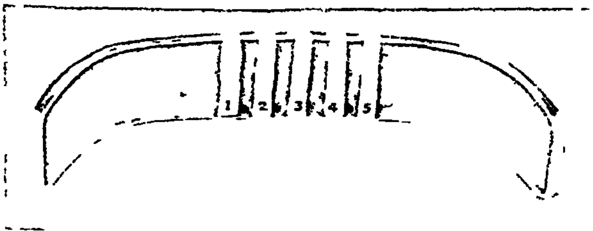

Fig 1—The icterometer

The icterometer (fig 1) is a strip of transparent perspex, $^1/_8$ in thick, $1^1/_4$ in wide, and 7 in long, curved at both ends for ease of handling On its convex surface are painted five transverse yellow stripes, in slightly different shades * These stripes and the spaces between them are $^3/_{16}$ in wide The stripes are numbered 1–5, the lightest in colour being 1, and the darkest 5

Method of Use

When the icterometer is used, the painted (convex) side is pressed against the tip of the baby's nose until the skin becomes blanched (fig 2) The yellow colour of the skin can then be matched with the yellow stripes on the scale The reading is recorded according to the number of the best match, or, if the colour falls half way between two stripes, as $1^1/_2$, &c

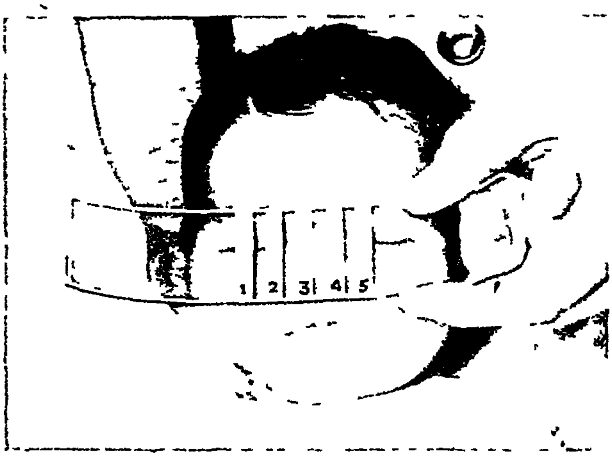

Fig 2—The icterometer in use

The nose is the obvious place for the test, because it is so easily accessible I have tried using other parts of the body but have found that readings were quite different

The instrument is washed with soap and water before being used on another baby Disinfectants or boiling could damage the perspex or discolour the yellow paint

The icterometer was originally devised in March, 1954, as a means of following the depth of jaundice in a baby from one day to the next In this it has been highly successful, for it shows at once whether the baby's skin is more or less jaundiced than it was the day before This is often all one wants to know It also enables the depth and duration of the jaundice to be permanently recorded, which may be invaluable later on

Correlation with Serum-bilirubin

In order to see how far the icterometer reading could be correlated with the serum-bilirubin level, a series of 229 comparative readings was made The results (fig 3) show broad agreement between the two methods, but the scatter is fairly wide, and one cannot deduce from a given icterometer reading what the serum-bilirubin level will be This is not surprising, because the series comprises many different babies, and the icterometer is influenced

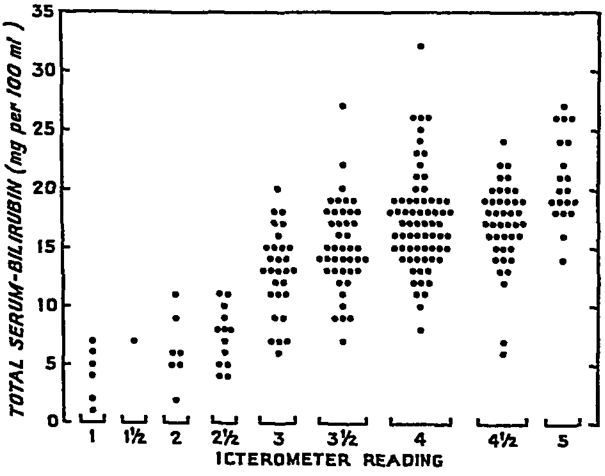

Fig 3—Icterometer readings compared with total serum-bilirubin levels (estimated by Molloy and Evelyn's method) Each dot indicates one reading

not only by jaundice but also by slight variations in skin colour between one baby and another

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* These were of 'Robbialac Colorizer' paint no 501, shades A, B, C, D, and E, made up in robbialac grey base undercoat

Fortunately one is much more concerned in practice with the interpretation of serial readings in single babies than with random sampling of the kind shown in fig 3, and my experience has been that when serial observations are made on individual babies from day to day, the serum-bilirubin levels and icterometer readings do in fact tend to rise and fall together

A Screening Test

Recording the intensity of jaundice in premature babies during the first week of life is important because an exchange transfusion may be necessary to prevent kernicterus Because the depth of jaundice cannot be judged by simple inspection, a great many babies are subjected to serum-bilirubin estimations to make sure of detecting the few at risk By using the icterometer as a preliminary screening test, some of these serum-bilirubin estimations can be avoided

At Northampton General Hospital we take 24 mg per 100 ml of total bilirubin (using the method of Molloy and Evelyn) as our threshold for replacement transfusion It follows that an accurate laboratory estimation of the serum-bilirubin is needed as soon as a level of about 20 mg per 100 ml is exceeded But fig 3 shows that in comparative tests no serum-bilirubin levels over 20 mg per 100 ml were encountered in babies with icterometer readings of 3 or less We have therefore made it our practice for the past $2^1/_2$ years not to ask for serum-bilirubin estimations until the icterometer reading is $3^1/_2$ or over, and we have no reason to believe that we have missed a case of kernicterus

Disadvantages

The icterometer is so simple that there are obvious snags

(1) The yellow stripes do not always give a perfect match with the baby's skin, but in practice this does not seem to matter, because different observers get closely comparable results

(2) It may not be reliable in artificial light

(3) It cannot be used for babies with bruised noses (e g, following face presentation)

(4) Its use is limited in black-skinned or yellow-skinned babies, in whom it will merely show whether or not the jaundice is increasing from day to day A Siamese baby, for example, had at birth an icterometer reading of 3, which rose gradually during the next few days to 5, and then fell back again to 3 and stayed there. This enabled us to spot her jaundice, and to say when it had passed its peak, but we had to invoke the laboratory to determine the extent of jaundice, because our scale was not calibrated for Siamese babies

(5) Milia on a baby's nose are a nuisance, but do not prevent the use of the icterometer

(6) When neonatal jaundice develops rapidly (as in blood-group incompatibility) the serum-bilirubin can rise so fast that the skin colour lags behind Hence babies developing jaundice within 36 hours of birth should always have their serum-bilirubin estimated, for in these circumstances it would be dangerous to rely on the icterometer as a screening test

(7) Cross-infection is an obvious possibility, but after more than 4 years the icterometer has not yet been incriminated The risk could be reduced by having a separate icterometer for each baby

(8) All the icterometers that I have used so far have been painted from five tins of robbialac paint made up in 1954 The colour shades of icterometers made from different batches of paint may not be identical with those I have described in this paper, although the makers of robbialac claim that their colorizer paints are standardised The same general principles will apply, however, and the colour differences are unlikely to interfere with the usefulness of the icterometer as a rapid cotside test

My thanks are due to the staff of the premature unit in the Barratt Maternity Home for testing and using the icterometer, to Dr D Phillpott and his laboratory technicians for their cooperation in calibrating it against the serum-bilirubin, to Mr J Pamely for fig 1, and to Dr W J A Hall Turner for his help in collecting the data for fig 3

Icterometers are now manufactured (using the original tins of paint) by Thos A Ingram & Co, Ltd, Santon Works, Prescott Street, Birmingham, 18, at a cost of 9*s* 6*d* each for quantities of a dozen For larger quantities the price will be lower

CLINICAL ASSESSMENT OF DEPTH OF JAUNDICE IN NEWBORN INFANTS

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Kernicterus, the most important complication of neonatal jaundice, has three main causes

(1) Rhesus incompatibility, where, because maternal blood-tests in pregnancy and the cord-blood findings at birth give reliable forewarnings, appropriate early exchange-transfusion can be undertaken

(2) ABO incompatibility, where Tovey et al (1959) found that the only important guides to treatment are the appearance of early jaundice and the frequent estimation of serum-bilirubin (to measure its approach to the potentially toxic level of 25 mg per 100 ml)

(3) Immaturity, the jaundice of which appears later but which requires the same control as that of ABO incompatibility (Crosse et al 1958)

Odell (1959) has suggested that kernicterus may depend upon the diffusibility of bilirubin, and that this may be determined by its degree of coupling with plasma-albumin, he further postulates that this may explain the occasional case of kernicterus at low serum-bilirubin levels

The relation of skin colour and serum-bilirubin has been the subject of discussion for many years

Davidson et al (1941) pressed a transparent tongue-depressor on the baby's skin and showed a qualitative relation between the degree of jaundice and the bilirubin level Allen (1958) described the value of polished lucite in the early detection of jaundice, although Lathe et al (1958) pointed out occasional high serum-bilirubin levels without apparent skin change It is well known that as jaundice fades the skin colour lags behind the serum-bilirubin level

A simple instrument, the icterometer, has been devised by Gosset (1960) to estimate the degree of skin icterus We have used this in an attempt to determine whether skin colour bears any relation to serum-bilirubin levels We set out to assess the value of this method as a screening test in neonatal jaundice, and, in view of the important observation of Davidson et al (1941) that one baby had a serum-bilirubin level of 12 1 mg without showing clinical jaundice, to assess the chances of missing a dangerously high level

ICTEROMETER READINGS CORRESPONDING WITH INDIRECT SERUM-BILIRUBIN LEVELS

Icterometer reading	No of observations	Serum-bilirubin (mg per 100 ml., indirect)		
		Mean	S.D	Range
2	4	5·55	1·61	3·9
2½	29	7 57	2 27	11 7
3	38	10·03	2 26	10 1
3½	66	12 31	2·50	12 3
4	27	15 73	3·03	11 7
4½	19	19 06	3·62	13 8

Method

Between December, 1958, and June, 1959, inclusive, there were 998 live births in the Birmingham Maternity Hospital Of these, 669 babies who remained in hospital for six days or more were available for synchronous icterometer and bilirubin estimations 165 babies were jaundiced, 59 being premature, and a total of 183 observations were made Those babies with fading jaundice, and those who had recently had exchange transfusions were excluded *Towards the end of the study only those* showing icterometer readings over 3 were included Icterometer readings observed by one, two, or three of us never varied by more than a half reading Blood was taken by venepuncture, or occasionally by heel prick, and bilirubin was estimated by the method of Lathe and Ruthven (1958) The differences between venous and heel-prick blood were not regarded as important in this correlation

Results

The icterometer readings corresponding with the indirect bilirubin levels are shown in the table together with the mean, the standard deviation, and the range. The relation between icterometer readings and the mean indirect bilirubin level is shown in fig 1

From these data fig 2 has been prepared to show the proportion of cases at or above a given bilirubin level that would be missed by taking a selected icterometer reading as a criterion

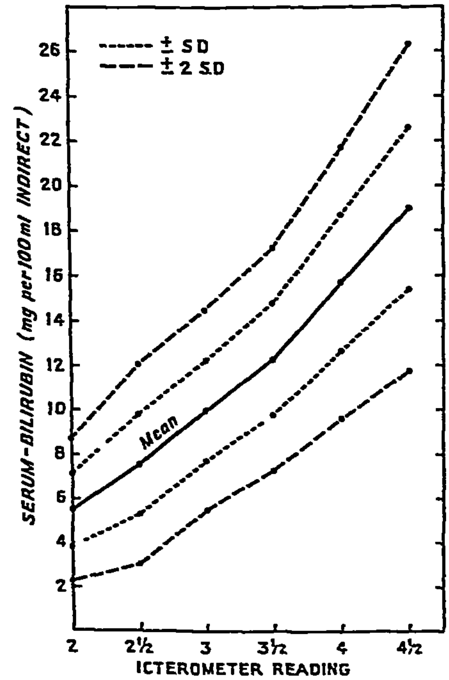

Fig 1—Relation between icterometer readings and the mean indirect bilirubin level.

Curves are drawn for three adjacent icterometer readings within the critical region, and they are related to indirect bilirubin levels Thus, for example, taking an icterometer reading of 3, only 1% of cases with an indirect level of 16 mg per 100 ml. or more will be missed.

Discussion

This simple instrument, which can be carried in the pocket and washed after use as one washes one's hands, seems to have a place in the nursery for the newborn Hitherto the timing of bilirubin estimations has depended on the unaided eye of the clinician, but this new instrument provides both a direct colour match and a means of expressing the blood, with the resultant pink colour, from the superficial skin layers Odell (1959) points out that measurement of the serum-bilirubin itself by present methods gives no indication of the degree of saturation of the serum-proteins with bilirubin, possibly, as a measure of diffusible bilirubin and the risk of kernicterus, the degree of skin pigmentation may be as good or even better

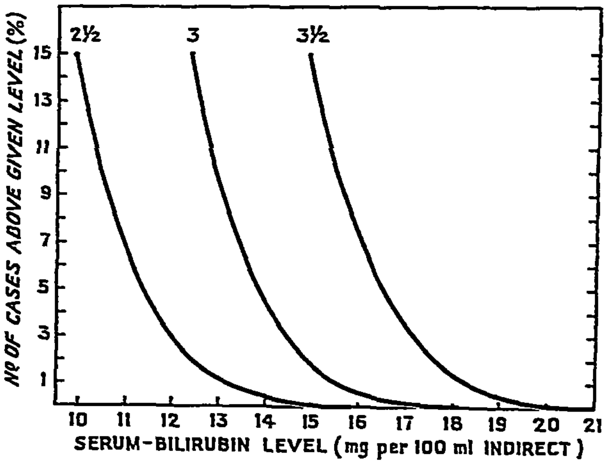

Fig 2—Proportion of cases above a given bilirubin level that would be missed by using the icterometer

For practical purposes our work suggests that, in cases other than those with rapidly increasing jaundice in the first twenty-four hours of life (such as in rhesus incompatibility), if the icterometer reading is 3 or below serum levels can be omitted, whereas above this reading blood studies should be undertaken Our observations were made in daylight, but artificial daylight lamps seem to give comparable results at night, and would be useful in a neonatal department

We are very grateful to Dr Dorothy Barrow for help with the clinical side of this work, and to Mr W F Johnson and Miss J M. Reynolds for performing most of the bilirubin estimations One of us (P E. C.) was in receipt of a grant from the United Birmingham Hospitals endowment fund.

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ANTERIOR-CHAMBER IMPLANTS IN OPHTHALMIC SURGERY

NEW DEVELOPMENTS AND NEW USES

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THE posterior-chamber acrylic* lens was described by Harold Ridley (1951) and the anterior-chamber implant by Strampelli (1954) Since the Strampelli type of lens was introduced into this country in 1956 it has been used to treat many hundreds of patients, and it is now recognised as a useful aid where uniocular aphakia cannot be corrected by a contact lens (*Lancet* 1958)

Eye injuries are not uncommon in childhood and when they result in uniocular cataract or aphakia the problem is urgent Amblyopia ex anopsia will probably complicate the picture within six to twelve months of the injury and is usually irreversible Very few of these young patients can be fitted with contact lenses within this period and the anterior-chamber implant offers the only opportunity of restoring reasonable visual acuity and binocular function

Some months ago I reported a series of 100 cases (Choyce 1959) In a second 100 I have used an implant differing in a number of respects from that originally designed by Strampelli The two most important differences are

1 Flattening of the anterior radius of curvature from 12 to 14 mm

2 Reduction of the thickness of the haptic portion from 0 91 to 0 50 mm

With this new thin implant the incidence of serious complications, such as endothelial corneal dystrophy, has been much lower These wholly transparent implants can also be used to treat, with success, cases of uniocular high myopia in young persons, but the climate of opinion in this country is against their use to correct binocular myopia or hypermetropia, because this can be adequately corrected by spectacles or by contact lenses

Obviously it would be an advantage if either the haptic or the optic portion of these implants could be made opaque, while the other portion remained clear The problem is how to tint or colour the polymethyl methacrylate of which they are composed

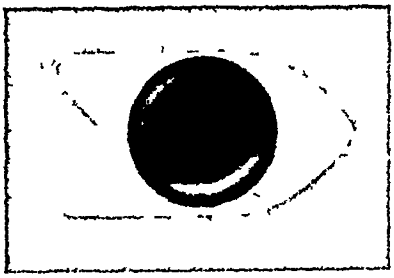

Fig 1—Anterior-chamber all-acrylic implant with transparent haptic and black optic the occlusive implant

Black perspex is readily made by introducing carbon-black, and it can be thermally fused with transparent perspex so that one can make an implant with a clear haptic and a black optic, or vice versa The result is a homogeneous piece of perspex (fig 1) which has the same mechanical properties as an ordinary implant and therefore will not break into its black and transparent portions after introduction into the eye

The implant with a black optic and a transparent haptic can be used to relieve intractable diplopia as in the following case

A patient with a severe anxiety state was referred by the psychiatrist because of diplopia Caused by a head injury in his teens, this remained constant and disabling despite numerous operations on the eye muscles The conventional shade over the squinting eye afforded no relief

Insertion of this occlusive implant relieved his diplopia and also his anxiety state For the first time in many years he is usefully employed and leading a contented home life If later he should need to make use of the sight in this eye, the implant can be removed

This type of implant can also be used to improve the appearance of a blind eye with an ugly complicated cataract such as is often seen after longstanding retinal detachment

The reverse of this type of implant—i e, with black haptic portion and a clear central optic—could be used in many cases where the iris is absent or deficient, but the large black pupil which would result would be very unsightly Imperial Chemical Industries were therefore asked to find some way of colouring the polymethyl methacrylate with pigments which would not diffuse into the eye and irritate it They have produced a partial answer in the form of perspex in three shades of blue and one shade of dark brown which (like black perspex) can be thermally fused with a clear central optic At the moment, matching a green iris is rather unsatisfactory Experience shows that, when inserted into the anterior chamber of a patient with a green or tawny iris, a brown haptic portion looks better than any of the blues

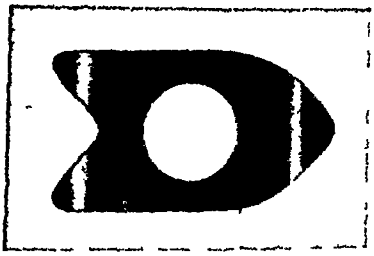

Fig 2—Anterior-chamber implant with coloured haptic and transparent optic for cases with iris deficiency

Thus the surgeon can introduce into the anterior chamber an implant which appears to fill in a coloboma of the iris with a haptic portion of appropriate hue If the coloboma is large, the diameter of the optic can be reduced to 2, 3, or 4 mm, thus sharpening the retinal image, as by the use of a stenopæic aperture (fig 2) If spherical ametropia is also present, a suitable correction can be moulded on the posterior surface of the central optical portion The following are examples of cases treated in this way

1 A youth of 16, with partial albinism, was also a low-grade myope Insertion of an implant, with brown haptic and a 4 mm optic with suitable myopic correction, has almost eliminated the photophobia from which he has always suffered The nystagmus is greatly reduced and the visual acuity, which was 6/60 with a myopic correction, is now 6/18

2 An engineer with a heavily pigmented brown iris sustained a perforating corneal wound with an iris prolapse, which resulted in a substantial temporal coloboma of the iris He suffered intense photophobia, not relieved by a tinted contact lens He had to wear a shade over this eye most of the time Insertion of an implant with a brown haptic has relieved the photophobia, and from a distance of a few feet the eye appears normal

3 A blue-eyed patient sustained a perforating wound in childhood which left him with a large iris coloboma above and temporally, and aphakia Before operation his corrected visual acuity was 6/60 After insertion of an implant with a dark-blue haptic and with an optical portion which corrected the aphakia, the photophobia has been eliminated and the visual acuity is 6/18

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* Acrylic = polymethyl methacrylate or 'Perspex'

Congenital aniridia seems to offer another promising field for the use of this type of implant

I am indebted to Mr P M. Caudell of the instrument department of Rayner Ltd., and to the plastics division of Imperial Chemical Industries, for their collaboration in the development of these new implants

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REDUCTION OF SPUTUM VISCOSITY BY A WATER AEROSOL IN CHRONIC BRONCHITIS

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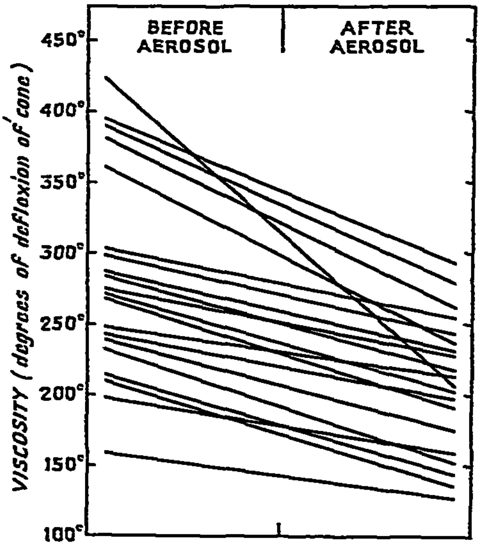
SPUTUM in chronic bronchitis is of two main kinds "mucoid", which is clear, gelatinous, and viscid, and "purulent", which is yellow, opaque, and less viscid Although purulence of sputum is shortlived when suitable antibiotics are used, mucoid sputum is not reduced by chemotherapy (May 1953), and persistent viscid mucoid sputum is an important manifestation of chronic bronchitis (Oswald 1954) Mucoid sputum is a mucoprotein gel, its viscosity depending on its mucoprotein content and the degree of hydration of the gel To reduce the viscosity of mucoid sputum, aerosol inhalation of enzymes and detergent solutions has been used (*British Medical Journal* 1954) Good results have been reported with solutions of trypsin (Unger and Unger 1953, Harwood Stevenson and Kinmer Wilson 1957), but others have thought it too irritant and have not been impressed by its mucolytic action in vivo (Farber et al 1954, Forbes and Wise 1957) Recently a less irritant derivative of trypsin—chymotrypsin—has been used by insufflation of the dry powder into the bronchial tree, with promising results (Robinson et al 1958)

The aerosol detergent used most often has been 'Alevaire' (which is a solution of a detergent with sodium bicarbonate and glycerin), and symptomatic benefit has followed its use, but a control solution containing water and sodium bicarbonate without detergent has been shown to facilitate expectoration as effectively as alevaire. Moreover, an hour's aerosol inhalation with either alevaire, the control solution, normal saline solution, or water is followed by a reduction in sputum viscosity of approximately equal degree (Palmer 1957) This suggests that these solutions owe their effect to their water content. I have, therefore, measured the effect of the aerosol inhalation of water on the viscosity of mucoid sputum in chronic bronchitics

Method

Twenty inpatient chronic bronchitics were admitted to the trial. Measurements were made in the afternoon because, in a period of control observation, the viscosity of the sputum was found to be most constant at this time

Each patient was studied for three hours In the first hour sputum was collected in a dry container and its viscosity measured (vide infra) In the second hour about 15 ml of water was nebulised in a 'Collison' or 'Oxygenaire' apparatus by oxygen In this way the water is administered as a fine "dry" mist with a particle size of 0 5–3 0μ. Sputum produced for one hour after the inhalation was collected and its viscosity measured. Patients were asked whether expectoration was easier after the inhalation, and improvement in rhonchi was noted.



Effect of water aerosol on viscosity of sputum.

Viscosity was measured in a cone and plate viscometer which was specially designed for this purpose (Palmer 1957) Viscosity is expressed in degrees of rotation of the cone—the deflection increasing with greater viscosity

Results

The results (see figure) show that there was a reduction in sputum viscosity in all twenty patients after the aerosol inhalation of the water mist for one hour, and that generally this was greatest where the initial viscosity was highest The mean reduction in viscosity was 71 4° (21 5%) (range 221–23°) All the patients felt that coughing was easier afterwards, and notable reduction in rhonchi was observed in many

Comment

An hour's aerosol inhalation of water reduced viscosity and greatly assisted expectoration in chronic bronchitics with viscid mucoid sputum Reduction in viscosity was greatest in those with the most viscid sputum, probably because the mucoprotein gel takes up water most avidly in this type of secretion.

This treatment is non-irritant, is devoid of toxic effects, and is physiological in action In this trial oxygen was used to aerolyse the water In patients with chronic bronchitis and emphysema and incipient respiratory failure (carbon-dioxide narcosis) continuous oxygen for an hour may be contraindicated (Westlake et al 1955) For these patients the water may be aerolysed by compressed air, or compressed air alternated with oxygen

Summary

In twenty chronic bronchitics with mucoid sputum, aerosol inhalation of a water mist for an hour reduced sputum viscosity and made expectoration easier

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AUTOIMMUNE HÆMOLYTIC ANÆMIA TREATED WITH VENOM ANTISERUM

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VENOM antiserum (' Antivenene ') is concentrated polyvalent anti-snake-venom serum, prepared at Haffkine Institute, Bombay, against the venoms of the four common poisonous snakes of India—i e , cobra, common krait, Russell's viper, and saw-scaled viper When injected intravenously with the venom into white mice each millilitre of the serum neutralises not less than the following quantities of dried venom cobra 0 6 mg , common krait 0 45 mg , Russell's viper 0 6 mg , and saw-scaled viper 0 45 mg If venom antiserum is given intravenously or intramuscularly the antibody in autoimmune hæmolytic anæmia is quickly removed, the antiglobulin test becomes negative, and hæmolysis ceases speedily

Material and Methods

Venom antiserum was given to twenty-seven patients, comprising twenty-two men and five women. Their ages ranged from 19 to 32 years, and the duration of anæmia was from 3 weeks to 2 years Twelve gave a past history of malaria 3–7 years previously, and seven had evidence of ankylostome infection, but antimalarial therapy and disinfestation before treatment with venom antiserum had not altered the course of the disease Two women were in mid-pregnancy Twenty-one patients were seen between the cold months of October and March. Four cases were acute, and the other twenty-three were chronic

A clinical as well as a serological remission, as in case 26 (vide infra), was desired. Venom antiserum was effective by both the intravenous and the intramuscular route, but the intravenous route was used for treating severe cases only It usually sufficed to inject 20 ml. of concentrated venom antiserum intravenously and 20 ml. intragluteally, the intramuscular injection being repeated on the 3rd, 7th, and 14th days of treatment. In very severe cases an additional intravenous injection was required on the 3rd day for complete clinical and serological remission In mild cases 20 ml of concentrated venom antiserum injected intragluteally on the 1st and 14th days was usually enough But sometimes complete serological remission was not obtained with this dose, as in case 11 (vide infra), and we now think an additional dose of 20 ml on the 3rd day is advisable

Results

The mild cases showed no further hæmolysis after the first injection of venom antiserum, and the blood-picture improved steadily

The severe cases showed a dramatic remission in constitutional symptoms within 48 hours of the first intravenous and intramuscular injections of venom antiserum, and the patient was well on the way to recovery within a week.

During follow-up for 5–26 months there were no clinical failures

Mode of Action

Venom antiserum was first used in the treatment of autoimmune hæmolytic anæmia because it prevented hæmolysis in blackwater fever (Singh and Singh 1944) Although it has always been effective in autoimmune hæmolytic anæmia so far, the mechanism by which it prevents hæmolysis is not yet absolutely clear The serological results in the following cases indicate that venom antiserum rapidly " removes " the antibody and potentiates in vivo an unknown protective mechanism

Case 26 (blood-group B) had a powerful, apparently nonspecific, agglutinin acting at the following titres

	37°C	*4 C*
Own cells	512	8192
Other cells	64	2048

The direct Coombs' test was positive No separable components for O, A_1, or B cells were present, the specificity of the autoagglutinin was unknown

5 days later, after a course of amodiaquine ('Camoquin'), which had been administered for suspected malaria, the antibody concentration was not significantly different, and the direct Coombs' test was still positive But 2 days after venom antiserum was given the antibody titre dropped appreciably

	37°C	*4°C*
Own cells	0	64
Other cells	0	16

and the direct Coombs' test was negative

Inhibition tests were made in vitro using the original sample of the patient's serum An ampoule of dried venom antiserum was reconstituted with 10 ml distilled water This solution was diluted 150 times to attain a concentration corresponding roughly to the serum level immediately after the intravenous injection of venom antiserum, and to inactivate agglutinins for human erythrocytes in the reconstituted venom antiserum Equal volumes of diluted venom antiserum and the patient's serum were mixed, left at room temperature for 30 minutes, and then tested against various erythrocytes, there was no inhibition of agglutination

Thus the therapeutic response to venom antiserum cannot be attributed to the direct inhibition of the autoagglutinin.

Case 11—The antibodies in the serum of this patient have already been described (Bird 1951) After a 2-week course of venom antiserum, given as for a mild case, her autoantibodies became active only at low temperatures 6 months later they were active against her own cells at 37°C, but she showed no signs of overt or masked hæmolytic anæmia, and the direct Coombs' test was negative Some in-vivo protective mechanism, therefore, seemed to be at work.

We are grateful to Lieut -General B Chaudhuri, Director-General, Armed Forces Medical Services, India, for permission to publish this report

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" if someone were to plead the virtues of an intellectually pastoral existence, not merely quiet but acquiescent, and with no more than a pensive regret for not understanding what could have been understood, then I believe I could listen to his arguments and, if they were good ones, might even be convinced But if he were to say that this course of action or inaction was the life that was authorised by Nature, that this was the life Nature provided for and intended us to lead, then I should tell him that he had no proper conception of Nature People who brandish naturalistic principles at us are usually up to mischief Think only of what we have suffered from a belief in the existence and overriding authority of a fighting instinct, from the doctrines of racial superiority and the metaphysics of blood and soil, from the belief that warfare between men or classes of men or nations represents a fulfilment of historical laws These are all excuses of one kind or another, and pretty thin excuses The inference we can draw from an analytical study of the differences between ourselves and other animals is surely this, that the bells which toll for mankind are—most of them, anyway—like the bells on alpine cattle, they are attached to our own necks, and it must be our fault if they do not make a cheerful and harmonious sound "—Prof P B MEDAWAR, *Listener*, Dec. 24, 1959, p 1118

THE LANCET

LONDON 9 JANUARY 1960

Poliomyelitis Vaccines

KILLED poliomyelitis vaccine can prevent paralytic poliomyelitis: this was demonstrated in a statistically sound controlled trial in the U.S.A.,[1] and subsequently confirmed in this country by a similar trial.[2] These trials showed that a primary course of vaccine was about 70% effective in preventing paralytic poliomyelitis (this means that the attack-rate in the vaccinated was 30% of that in the unvaccinated). There were, therefore, high hopes that poliomyelitis would dwindle into clinical and epidemiological insignificance, although many authorities still believed that the final answer might be an attenuated vaccine—mainly because of doubts about the duration of immunity conferred by killed vaccine. A living vaccine is thought likely to give a durable immunity because of the finding of PAUL et al[3] that poliovirus antibodies apparently persisted for forty years in an isolated Eskimo population, and a living vaccine has been favoured because yellow fever and smallpox are successfully controlled in this way (though the immunity after smallpox vaccination is not lifelong). On the other hand, poliovirus neutralising antibodies fall in titre during convalescence at very much the same rate as they decay in people vaccinated with killed or attenuated virus,[4-6] so the superiority of living vaccine in this respect cannot be taken for granted.

Unfortunately, despite the widespread use of killed vaccine, there have been several substantial outbreaks of poliomyelitis, especially in the U.S.A.: in 1959 there were almost certainly as many paralytic cases in the U.S.A. as there were in 1956. This situation has led to disquiet lest the vaccine should be proving less effective than was to be expected from the Francis report,[1] and it has also stimulated intense interest in attenuated-virus vaccines. Soon after the Francis report appeared, the Cutter disaster led to changes in manufacturing and safety-testing requirements for killed vaccine. It is clear that these changes produced a safe product—but was potency sacrificed? There is some evidence that the antigenic potency of American vaccines has declined: for example, SALK[7] has found, in a survey of children in Pittsburgh, that the antibody response in 1956 was much superior to that in 1958. Similarly, other workers in the U.S.A. have reported very low levels of antibody response in children. In BARR's experience[8] more than 50% lacked antibodies to type-1 and type-3 virus after three doses. Fox et al[9] recorded similar experiences and also found that Salk vaccination did not appear to prevent natural infection of the alimentary canal with polioviruses, whereas naturally acquired antibodies did prevent infection. This difference is probably due to differences in circulating antibody titre, but it has been suggested that a local alimentary immunity conferred by natural and attenuated virus infection is responsible.[10] The vaccine used in the Medical Research Council trials in this country, which assessed both antigenic potency and effectiveness in preventing paralysis, was made with material that had passed the more stringent control tests introduced in this country after the events in America. The impression that killed vaccine may be less effective than had been expected was to some extent supported by preliminary data published by the U.S. Communicable Diseases Center in poliomyelitis surveillance reports, which showed substantial numbers of cases in individuals given three doses of vaccine. Recently, however, a new report[11] gives reassuring preliminary figures of vaccine effectiveness. From census figures and an extensive sample survey of immunisation status, age-specific attack-rates for unvaccinated and vaccinated individuals were calculated. From these figures the effectiveness of the vaccine can be estimated. In 1958 and the first 45 weeks of 1959 for age-groups up to 14 the estimates exceed 90% against paralytic poliomyelitis for those given three or more doses of vaccine. It must be emphasised that the results are preliminary, especially those for 1959. Two important confusing factors are present: for 1959 the diagnosis of paralytic poliomyelitis has been accepted although revision of the diagnosis in some cases is probable at the 60-day follow-up report, and there is considerable heterogeneity in the immunisation status of the population. Thus, a protection-rate calculated on the basis of the overall national immunisation-rate may overemphasise the protective effect of vaccine for poorly vaccinated population subgroups. Similarly, both the national immunisation surveys were carried out in September, which may boost the apparent effectiveness, since unvaccinated people who succumb early in the year would count in the unvaccinated attack-rate, yet those who escaped paralysis in an early epidemic and were subsequently vaccinated would be counted as vaccination successes. The effect of errors of diagnosis would be mainly to include cases presenting with paralysis which were not due to poliovirus. This source of error might, therefore, to some extent counterbalance the effect of different vaccination-rates. It is probable, however, that some cases of apparently non-paralytic poliomyelitis would have to be added to the paralytic group after follow-up. There is some evidence that the viruses isolated from both paralytic and non-paralytic cases are less likely to be poliovirus (and more likely to be other enteroviruses) in vaccinated than in unvaccinated people. LENNETTE et al[12] report that poliovirus was isolated from 81% of unvaccinated patients with paralytic poliomyelitis under 5 years of age and other enteroviruses from 2%, whereas the isolation-rate was 36% for polioviruses and 21% for enteroviruses in infants who had had two or more doses of vaccine

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Although the exact figure of effectiveness may be subject to revision, it is unlikely that it will prove seriously wrong since it is confirmed in a preliminary study of a major outbreak in Des Moines The estimates of vaccine effectiveness exceed 85% for three doses for 3 separate population groups (Negroes and lower and middle socio-economic white groups), based on immunisation surveys early in the epidemic The mere concentration of cases in the least vaccinated groups—for example, the majority of cases were in the 0–4 year age-group and in Negroes (in the whole U S the rate for Negroes is twice that in whites and in localised epidemics is up to 15-fold higher)—provides prima-facie evidence of high vaccine effectiveness

It seems, therefore, that there are good grounds for believing that the killed vaccine has proved highly effective, but that immunisation programmes have proved less so Some of the proponents of attenuated vaccine have argued that the capacity of these attenuated strains to spread in the community and therefore to vaccinate involuntarily some of those reluctant to accept parenteral vaccine might be a positive advantage Moreover, they point out that killed vaccine has failed to halt the progress of several outbreaks,[13] and they contend that attenuated vaccine may well be effective under these conditions, not only by producing antibodies more rapidly but also by producing interference in the alimentary tract before active immunity is acquired Indeed, it has been suggested that epidemics may end not by exhaustion of susceptibles but by the emergence of attenuated viruses All this is, for the moment, supposition The best way of combating an epidemic of poliomyelitis is probably the method of passive and active immunisation found so successful for diphtheria [14] It is known that gamma-globulin is effective in preventing poliomyelitis [15], indeed, when used for treatment, gamma-globulin of very high titre has mitigated the severity of experimental poliomyelitis in monkeys [16] Combined gamma-globulin and poliovaccine, perhaps in larger doses,[17] should therefore prove effective

Recently MELNICK and his colleagues [18] examined some of the candidate strains for inclusion in attenuated vaccine They found both Sabin and Lederle strains to be more virulent than expected They also found evidence that Sabin strains (which were the most attenuated) could undergo mutation to substantially greater virulence during passage in man The difficulties of conducting an adequate trial of safety when virulent virus causes only 1 clinical case in 100–500 infections are considerable There are also formidable technical difficulties of manufacture to face in order to establish consistently safe vaccine when the virus is mutable and the tissue used to cultivate it is potentially contaminated with numerous viruses [19] These viruses, except virus B, which is a fatal human pathogen, are of unknown effect in man The remarkable properties of the newly discovered S E polyoma [20] virus should perhaps be a warning against dismissing these viruses from consideration as human pathogens In view of these manufacturing and testing difficulties, the great economies which it was hoped might follow from the use of living vaccine may prove illusory, but the difficulties have been no deterrent to the mass programme already completed, particularly in Russia and Eastern Europe In Russia, where Sabin strains have been used, over 10 million people have received all three types of virus, and neither here nor elsewhere has there been any suggestion that poliomyelitis has been caused by any of the strains of attenuated virus The attenuated vaccine will probably prove effective provided there is not too much interference with the establishment of the poliovirus infection by other enteroviruses, as has been noted, for example, by HORSTMANN et al [21] MELNICK et al, however, plead for caution in the development of attenuated vaccines The introduction of killed vaccine required caution, and yet disaster was not wholly avoided greater caution is called for in introducing a vaccine known to be able to spread uncontrollably in the community And the need for care is further underlined by the apparently reassuring figures of the efficacy of killed vaccine It may be that killed vaccine can be made more widely acceptable by the use of combined antigens, which are being effectively given in Canada [22], and this would also have advantages in reducing the number of injections—a change that would be attractive to children, mothers, doctors, and the Chancellor of the Exchequer

Breech Presentation and Delivery

UNDER the most favourable circumstances fœtal loss associated with breech delivery is very low COX [23–25] has shown that at the Liverpool maternity hospital the fœtal mortality in uncomplicated cases has fallen steadily until now several resident obstetricians from that hospital can claim large personal series of deliveries with a fœtal loss below 1 5% These excellent results come from a teaching hospital which has long taken great interest in the management of breech delivery It is encouraging to learn from DALEY and MICHAEL [26] and HAY [27] that in non-teaching hospitals, even where breech deliveries are carried out by different people over the years, equally good results are attainable To some extent such results reflect a tradition passed from one generation of resident staff to another, but much of the credit must lie with the senior consultant staff who are ultimately responsible for standards It would be unrealistic to claim that hospital management of breech delivery is generally associated with such good results, but the available evidence suggests that confinement in hospital is safer than at home Cox,[23] in his account of breech delivery in Liverpool in 1933–49, reported a fœtal mortality of 20% among 120 cases of uncomplicated breech delivery carried out by midwives in the patients' homes this despite the fact that the midwives were well trained in the Liverpool technique of delivery It is impossible for anyone, single-handed, in domiciliary surroundings to compete with the results obtained by a team in a hospital labour ward Nevertheless, some doctors and midwives still consider that a multiparous breech delivery can safely be conducted at home This is a dangerous belief, for there is good evidence [23 26 28–30] that the risk to the fœtus is greater in multiparous than in primiparous breech delivery

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In order to assess fœtal mortality associated with breech delivery, Cox and others have excluded from their final figures cases complicated by such factors as placenta prævia, twin pregnancy, prematurity, and prolapse of the cord Although this arrangement is helpful, not all workers agree about which cases should be considered "complicated" and therefore excluded some maintain that prolapse of the cord, contracted pelvis, or long labour should be regarded as part of the intrinsic risk to the fœtus The Royal College of Obstetricians and Gynæcologists [31] gave some guidance on this point in 1948, but there is need for further clarification

Opinion remains divided on the advisability of external version Twenty-five years ago WRIGLEY [32] reported a fœtal mortality of 13% when the manipulation was applied under anæsthesia today the figure is likely to lie somewhere between 1 and 2% [33 34] Without anæsthesia the risk to the fœtus is significantly less [35–37] In modern obstetric practice, where fœtal survival in uncomplicated breech delivery can be 98%, the place of external version, particularly under anæsthesia, must be reviewed very carefully When the patient is to be delivered in a large maternity unit by a skilled team much can be said for WHITE's [30] view that external version should be reserved for patients with slight or moderate pelvic contraction When external version fails and there is some doubt about the fœtal-pelvic relationship, an important decision about the mode of delivery has to be made Some obstetricians, with X-ray confirmation of even minor pelvic contraction, would favour elective cæsarean section, but where the disproportion is borderline the majority would probably be prepared to allow a trial of labour The experienced observer can learn much, under these circumstances, from the pattern of uterine contractions and the progress of labour With good pains and steady descent of the breech to the pelvic outlet there is every likelihood of a safe vaginal delivery Abnormal uterine action and failure of the breech to advance point to significant disproportion and the need for cæsarean section HAY, in his series of cases from St. David's Hospital, Bangor, reports that cæsarean section was carried out in 16% and suggests that this is in keeping with modern obstetric practice. In fact, the need for cæsarean section in breech presentation will vary from one hospital to another Hospitals deal with selected clinical material, and the rate of cæsarean section will depend on the ages, stature, and parity of the patients and the weights of their babies and is likely to be high when there are many emergency admissions Study of a total community would give a much truer picture of the management and results of breech presentation in any particular area and would make valid comparisons possible Unfortunately, there is at present little enthusiasm for such an epidemiological approach to obstetrics

The survival and well-being of the baby depend largely on the judgment and manipulative skill of the person who conducts the delivery The best results for mother and baby will certainly be obtained in a well-run maternity hospital where obstetrician, anæsthetist, and pædiatrician work as a team in favourable surroundings But domiciliary practice will always include cases of breech presentation undiagnosed before the onset of labour When the diagnosis is made early in labour there is everything to be said for transferring the patient to a suitable hospital When the presentation is recognised late in labour, this should be regarded as an emergency and the obstetric flying-squad summoned

Ultrasonics in Ménière's Disease

THE symptom-complex of paroxysmal rotatory vertigo with deafness and tinnitus has long been recognised as a disabling condition. PROSPER MENIÈRE brilliantly deduced its pathology by correctly interpreting the work of his colleague FLOURENS, who in 1842 observed disorders of equilibrium in pigeons after injury to the semicircular canals As early as 1883 WOAKES [1] advanced the hypothesis that it was associated with increased intralabyrinthine tension—a hypothesis which was finally confirmed in 1938 by HALLPIKE and CAIRNS [2] in their classic description of the distended endolymphatic system in the labyrinth affected by Menière's disease.

No wholly satisfactory method of treatment has yet been devised This failure is due to several reasons the labyrinth is enclosed in a capsule of hard compact bone within the petrous pyramid, which makes any direct observations on its delicate neuroepithelium very difficult, the disease itself is never lethal, so opportunities for postmortem study are rare, and assessment of therapeutic results is difficult because spontaneous remissions are common and may last for many years Mental strain is said to foster attacks, possibly through sympathetic-parasympathetic imbalance resulting in hydrops of the labyrinth But, while emotional stress is often evident in Menière's disease, this is to be expected in a condition where a fit person is suddenly struck down with acute vertigo at unpredictable moments In treatment simple sedation, vasodilators, histamine, vitamins, diets, and anti-histamine drugs are all used singly or in combination Relief of symptoms followed by remissions is achieved in a high proportion of cases, but in most

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28 Cutts, R., Abbas T M *Edinb med J* 1951, 58 35
29 Redman T F *Brit med J* 1950 i, 814
30 White A J *J Obst et Gynæc Brit Emp* 1956 63 706
31 Royal College of Obstetricians and Gynæcologists *ibid* 1948, 55 478
32 Wrigley, A J *Brit med J* 1934, i 801
33 Peel J, Clayton S G *J Obstet Gynæc Brit Emp* 1948, 55 614
34 Freeth, D Macvine, J S *Brit med J* 1951 ii, 881
35 Ryder, G H *Amer J Obst et Gynec* 1943, 45 1004
36 Siegal I A, McNally H B *Sth med J* 1951, 44 942
37 Macafee, C H G, McClure, H I *Brit med J* 1937 ii 1117

1 Woakes E *Brit med J* 1883 i 801
2 Hallpike C S, Cairns, H *Proc R Soc Med* 1938, 31, 1317

published series gradual deterioration of hearing in many cases, and development of the disease on the other side in some, have been noted Surgery is indicated when medical treatment has failed, and should be undertaken without undue delay Three main types of operation are in use intracranial section of the vestibular fibres of the eighth cranial nerve, destruction of the labyrinth, and sympathectomy In most cases the paroxysmal vertigo is relieved by the first two methods The hearing is totally destroyed by any direct operation on the vestibular end-organ, and it is often damaged by partial section of the eighth nerve Sympathectomy was introduced to preserve the hearing, but it does not always control the vertigo As Menière's disease becomes bilateral in 10–30% of cases, great efforts have been made to devise treatment that is effective and yet does not impair the hearing

The possibility of applying ultrasonic frequencies to a restricted part of the inner ear, without damaging adjacent structures, was demonstrated by **Krejci** and **Bornschein**[3], and **Lumsden**[4] has now described his experience of ultrasonic ablation of the vestibular end-organ Ultrasonic waves do not pass from air to a solid or liquid medium (or vice versa) because they are reflected at the interfaces The bony external semicircular canal is therefore exposed surgically and ultrasound applied directly to the canal The irradiation is directed so that both the cochlea and the facial nerve are avoided Ultrasound may act by means of its mechanical, thermal, or chemical effects, but its precise mode of action on the labyrinth has not yet been established this is one objection to its routine use Undoubtedly, however, tissue destruction results from the application of suitable ultrasonic doses, and this constitutes a difficulty in clinical practice, where dosage must be based on the inexact signs of nystagmus and on previous experience **Arslan**[5] has reported the biggest series hitherto in six years' follow-up 95% of patients were free of acute vertigo and the majority had unimpaired hearing **Lumsden** found that in the first few weeks after operation modified attacks of vertigo might occur while the degeneration of the labyrinth became complete, continued vertigo usually denoted an inadequate dose A second application sometimes controlled the symptoms Facial palsy is the most important complication, but in all the reported cases spontaneous recovery has ensued The effect of ultrasound on persistent tinnitus is somewhat unpredictable, but **Arslan** seems to have had more success than some other workers

A good deal of work on the effects of ultrasound in Menière's disease remains to be done But, though still in the experimental stage, ultrasonic ablation of the labyrinth is already worth considering in cases with good hearing that do not respond to medical treatment, or where the patient is already deaf in the other ear from previous disease, labyrinthectomy, or other causes Ultrasound may eventually prove superior to all other forms of treatment[6,7]

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[3] Krejci, F, Bornschein, H *Arch ital Otol* 1951, 62, 1
[4] Lumsden R B *Scot med J* 1959, 4 519
[5] Arslan, M *Sci med ital* 1958, 7, 301
[6] Dubs, R *Pract oto-rhino-laryng* 1957, 19, 401
[7] Altman F Waltner, J G *Arch Otolaryng, Chicago*, 1959, 69, 7

Annotations

SEWAGE AND THE BATHER

For some years concern has been expressed in Parliament and in the Press about the risk of contracting infectious diseases (and especially poliomyelitis) by bathing in seawater polluted by sewage A committee of the Public Health Laboratory Service has for some years been inquiring into this danger and its findings have now been published in a scientific report[1] and an abbreviated version thought suitable for politicians and journalists[2] Having reviewed evidence from many sources, the committee can say without qualification that there are no grounds for thinking that bathing in the sea involves any appreciable risk of diseases

The most popular beaches are those adjacent to large towns, and almost all these towns discharge their sewage into the sea Most samples of water from these beaches show clear evidence of fæcal pollution and some contain *Salmonella spp* in small numbers Technical difficulties make the hunt for poliovirus very difficult, but there is no reason to doubt its presence along with the other fæcal organisms The chief virtue of discharging sewage into the sea is that it is quickly diluted, and to this dilution the bathers owe their freedom from infection Except for *S typhi*, the dose of salmonellæ needed to produce disease in man is large, and, for reasons not yet fully understood, human pathogenic bacteria do not survive very long in seawater On the epidemiological side the evidence is scanty—partly because the person who has bathed has probably also eaten ice-cream, winkles, and fish-and-chips—to say nothing of looking at the peepshows on the pier

One of the major tasks of the committee was the collection of bacteriological data—counts of coliform organisms and fæcal coli—from many beaches The interpretation of these is difficult No two beaches and no two sewage outfalls are alike The vagaries of local tidal currents are unpredictable without long experience and exact tests with floats or radioactive tracers Dilution is not immediate and its efficacy will obviously depend on the distance of the sampling-point from the outfall and upon the temporary effects of wind and waves At no point within the range of the sewage outfall can the water be considered as a homogeneous fluid, and a difference of an hour (in relation to high water) can give very different bacteriological results For this reason the committee rejects the idea of a standard of bacteriological purity for bathing-beaches similar to that used for drinking-water Such standards exist in a few places in the U S A., and there is no evidence that they have had any effect on the public health or that they are enforceable The bacteriological survey has, however, some uses Sampling at short intervals along the beach, continued for many months in all sorts of weathers, will give a reasonable idea of the amount of fæcal pollution and may be essential in judging the need for a new outfall or assessing the results of such an improvement. But—like a bacteriological finding in clinical medicine—it means very little unless it is considered in conjunction with all the other factors involved, and a few unplanned and irregular tests can only be misleading To compare the health-giving properties of Brinyville and Foulwater Bay by such tests is dishonest

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[1] Report. *J Hyg, Camb* 1959, 57, 435
[2] Medical Research Council Memorandum no 37 H.M Stationery Office. 1959 Pp 24 2*s* 6*d*

So far so good, and it is satisfactory to know that one potential source of risk to health has been given an approximate quantitative value. We hope, however, that this report will not be used as an excuse for making our beaches even more foul than they are today. The population of seaside towns is increasing above the average rate, and more people spend more time on the beach. Because fæces and toilet-paper are not yet common objects of the seashore is no excuse for a practice which is almost always dictated by cries for economy. It is true that a greater danger to health and natural beauty comes from the pollution of our estuaries (about which the committee was not concerned). The dilution factor in an estuary is variable, affected by wind, water, and the flow of fresh water, and usually insufficient. An oversight by the legislators of the last century allowed estuaries to be treated as the open sea, and the result is only too obvious in the Thames, the Dee,[3] the Tyne, and fifty other rivers. As a factor in robbing the water of oxygen, sewage is ancillary to industrial effluents, and the result is a fluid which will support no form of life—except bathers. (There is no more popular bathing-place in London than the plage just above Tower Bridge.)

The committee did not consider the dangers of bathing in fresh water, and about this we know very little. The Thames Conservancy forbid the discharge of excreta from any boat on their waters and enforce this by-law strictly. Other bodies with similar problems should follow the Conservancy's example. The danger of catching typhoid by bathing in the Norfolk broads may be small, but nobody knows how big it is. We must be grateful to this committee for pointing out the way in which these and many similar problems can be tackled.

IMMUNOLOGICAL UNRESPONSIVENESS

Recent interest in the possible role of autoantibodies in the pathogenesis of some human diseases has been a considerable stimulus to work on fundamental processes of antibody production. In this category is the study by Crampton, Frankel, and Rodeheaver[4] on the mechanism of immunological unresponsiveness. Such a state of specific unresponsiveness can be induced in several species of animal by repeated injections of large amounts of the appropriate antigen[5, 6], and by the use of antigens labelled with radioactive iodine Crampton and his colleagues sought to demonstrate the difference, if any, in distribution of the antigen in responsive and unresponsive animals. No such differences were detected, the antigen in both series of animals being found in intracytoplasmic granules in the liver and spleen. Crampton et al. have, therefore, suggested that the condition of immunological unresponsiveness may result from the destruction of the specifically stimulated cells by an intracellular antigen-antibody reaction. As long as an excess of antigen is made available it is presumed that sufficient free antigen will be contained in the antibody-producing cells to encompass their own destruction. With the relatively minute quantities of antigen usually used to stimulate antibody formation the quantity of antigen within some, at least, of the stimulated cells is presumably too small to be lethal.

The distinction between immunological unresponsiveness and immunological tolerance is noteworthy: unresponsiveness is brought about and maintained by repeated injections of large quantities of antigen at almost any period of life; tolerance is a more or less permanent state induced by the injection of living cells within a very short period of birth.[7] Since the persistence of tolerance also requires the survival of the injected foreign cells or their descendants the final mechanism may well be the same—namely, self-destruction of the specifically stimulated cell, the result of intracellular reaction of antigen and antibody.

A particularly attractive feature of this hypothesis of Crampton et al. is the explanation that it affords of the differences between a primary and a secondary response. Thus, following primary stimulation by a small amount of antigen the antibody that subsequently appears in the plasma is the product of those specifically stimulated cells that have survived any intracellular antigen-antibody reaction. Whatever is the precise nature of these cells when first they make contact with antigen they subsequently acquire the cytological characteristics of plasma cells, and thus have apparently lost the ability to take up antigen intracellularly. Since they continue to secrete specific antibody protein it is reasonable to assume that they are still capable of reacting specifically with any future access of antigen. It is postulated, however, that such a surface interaction results, not in death, but in stimulation to proliferation. The secondary response is therefore characterised by both its speed and its magnitude.

A slightly different but even further reaching hypothesis was put forward by Burnet in 1957.[8] This too requires that according to circumstances the antibody-forming cells are killed or excited to reproduce. The recent work of Crampton and his colleagues offers a plausible explanation of the way in which these strikingly different results could be brought about.

THE GAMMA SYSTEM IN MAN

The gamma system comprises the small-diameter efferent nerve-fibres which originate from small anterior-horn cells, together with the intrafusal muscle-fibres which they supply within the muscle spindles. As Leskell[9] originally showed in cats, this system can change the sensitivity, or bias, of the primary (annulospiral) sensory endings to imposed stretch. Subsequently both the functioning of the gamma system and its supraspinal control have been intensively studied. Apparently, in many postural reflex contractions of striated muscle, nerve impulses are initially routed from the spinal cord via the small efferent fibres to produce a shortening of the intrafusal muscle-fibres. This shortening stretches the primary sensory endings and increases their afferent discharge. The resultant enhanced bombardment of large anterior-horn cells leads to contraction of the extrafusal striated muscle-fibres, which diminishes the spindle afferent discharge. The primary sensory endings here operate as null detectors, discharging afferent impulses at a rate which is proportional to the differing lengths of the intrafusal and extrafusal muscle-fibres. This conception of the muscle-spindle's function enlarges the earlier view that the spindle acted merely as a detector of muscle stretch, though both of these activities ultimately depend on stretch of the primary sensory ending. Merton[10] further suggested that the gamma system might play an essential part in the execution of certain willed movements He postulated that descending impulses from the supraspinal centres controlling willed movements might be routed to the small anterior-horn cells and thus produce willed contraction of striated muscles over the same pathways as those of postural reflexes

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[3] *Lancet*, 1959, i, 927.

[4] Crampton, C. F., Frankel, F. R., Rodeheaver, J. L. *Nature, Lond.* 1959, 184, 873.

[5] Dixon, F. J., Maurer, P. H. *J. exp. Med.* 1955, 101, 245.

[6] Boyd, W. C. Fundamentals of Immunology. New York, 1956.

[7] Billingham, R. E., Brent, L., Medawar, P. B. *Nature, Lond.* 1953, 172, 603.

[8] Burnet, F. M. *Aust. J. Sci.* 1957, 20, 67.

[9] Leskell, L. *Acta physiol. scand.* 1945, 10, suppl. 31.

[10] Merton, P. A. in The Spinal Cord (edited by J. L. Malcolm, J. A. B. Gray, G. E. W. Wolstenholme, and J. S. Freeman). London, 1953.

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From all this work it seemed that the gamma system might be of considerable importance in man Many of the observations on man are based on a finding of Hoffmann [11] that the medial popliteal nerve may be electrically stimulated in such a way as to produce a pure reflex contraction of the gastrocnemius-soleus muscle-group This H reflex [12] was thought to follow the same reflex pathway as the ankle-jerk, but to differ from the tendon reflex in so far as the muscle-spindles (and the associated gamma efferents) were removed from circuit Differences in the responses of the ankle-jerk and the H reflex could thus be equated with the degree of activity in the gamma system

Sommer [13] observed that Jendrassik's reinforcement potentiated the ankle-jerk while leaving the H reflex unaltered, the experiments were repeated by Paillard,[14] and reinforcement has been ascribed to enhanced activity of small motor-fibres leading to increased sensitivity to stretch of the primary spindle-endings Similarly Buller [15] suggested that the hyperreflexia of early hemiplegia is due to resetting of the muscle-spindles on the abnormal side, and Benson [16] has argued that some labyrinthine reflexes are effected via the gamma system The validity of all these arguments rests on the assumption that the central reflex pathways of the ankle-jerk and the H reflex are identical. But Magladery and Teasdall [17] have shown that in man probably neither the ankle-jerk nor the H reflex pursue purely monosynaptic paths, and they have questioned whether the ankle-jerk and H reflex do follow identical central pathways If the pathways are different—if, for example, the spinal pathway subserving the ankle-jerk includes an interneurone which is not also activated during elicitation of the H reflex—then supraspinal control of that intraneurone [18] might explain the differences between the tendon-jerk and H-reflex responses attributed by Sommer,[13] Buller,[15] and Benson [16] to gamma-system activity Thus, while the observations of these three workers suggest that the gamma system is functionally important in man, they do not prove it

Further indirect evidence of the existence of tonic gamma-system activity during the waking state is provided by the observation of Buller and Dornhorst [19] that local infiltration round the medial popliteal nerve with cinchocaine abolishes the ankle jerk while leaving the H reflex unaltered By analogy with the differential gamma-fibre blocks produced in the cat with procaine,[20] Buller and Dornhorst suggested that they had selectively blocked the gamma efferent fibres to the muscle-spindles supplied by the medial popliteal nerve If this is correct, it would seem that in the waking state the intrafusal muscle-fibres are continuously under gamma control, and therefore probably accessible to reflex or supraspinal control

All these observations on man have been concerned with the tendon-jerk The gamma system also takes part in determining the static stretch reflex, which is estimated clinically as muscle tone That the tendon-jerks and muscle tone may vary independently is known from clinical experience, and has been clearly shown by Hammond [21] The explanation of this independence probably lies in the separate supraspinal control of synapses on the central pathway for tone which do not form part of the spinal pathway of the tendon reflex Such synapses may be at interneurones and/or Renshaw cells While the discharge from the muscle-spindle (itself determined by gamma activity) is important in determining both the tendon reflex and muscle tone, differences in the intraspinal pathways of these two reflex arcs allow independent supraspinal control

Thus, in man there is indirect evidence that the gamma system plays a part in both the phasic and the static reactions of the stretch reflex It seems likely that gamma efferent activity is maintained throughout the waking state and may be modified as part of normal postural reflex activity, and also as a result of damage to the central nervous system The part played by the gamma system in willed movement is still unknown

NEW YEAR HONOURS

In recognition of his presidency of the Royal College of Surgeons, Sir James Paterson Ross receives a baronetcy Even before his election, Sir James did much for the college in the congenial role of dean of the Institute of Basic Medical Sciences, and in the difficult period of financial reconstruction that has coincided with his term of presidential office the college has been fortunate in having at its head a man so much respected alike as a surgeon, as a teacher, and as a person Similarly, as president of the Royal College of Obstetricians and Gynæcologists, since 1957, Prof Andrew Claye has given a great deal of time and thought to its development, and his knighthood will give pleasure both on public and on personal grounds Dr Ivan Magill, who is promoted to a knighthood in the Royal Victorian Order, is one of the innovators who have created modern anæsthesia, and by his tubes, his laryngoscope, and his rebreathing bag his name is known wherever this art and science are practised As a practical prophet, he is very far from being without honour in his own country Prof Derrick Dunlop not only has been chairman of the British Pharmacopœia Commission, and much else that officially justifies his knighthood, but also is a great Edinburgh personality and memorable teacher Moreover, unlike so many knights nowadays, he lives in a real castle In Australia, Sir Charles Blackburn, who is created K C M G, was knighted in 1936 and has been chancellor of the University of Sydney since 1941 he is consulting physician to the Royal Prince Alfred Hospital Of the knights bachelor, Prof Edward Ford became director of the School of Public Health and Tropical Medicine in Sydney in 1947, having done much work in the Army which his colleagues rated especially high, and Dr W W S Johnston, who has a fine record during and after both world wars, has been consulting physician to the Royal Melbourne Hospital, and chairman of the Melbourne Permanent Postgraduate Committee, for four years Prof J P Walsh, now K B E, is dean of the University of Otago Dental School

The remainder of the list published on p 106 contains the names of many other medical men and women who are held in high regard by those who work with them and by those for whom they work

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[11] Hoffmann P *Z Biol* 1920, 70, 515
[12] Magladery J W, McDougal, D B *Bull Johns Hopk Hosp* 1950, 86, 265
[13] Sommer, J *Dtsch Z Nervenheilk* 1940, 150, 249
[14] Paillard, J Reflexes et regulations d origine proprioceptive chez l homme Paris, 1955
[15] Buller, A J *Lancet*, 1957 ii 1262
[16] Benson, A J *J Physiol* 1959 148, 37P
[17] Magladery, J W, Teasdall, R D *Bull Johns Hopk Hosp* 1958, 103, 236
[18] Eccles, R M Lundberg, A *J Physiol* 1959 147, 565
[19] Buller, A J, Dornhorst, A C *ibid* 1958, 145, 12P
[20] Matthews, P B, Rushworth, G *ibid* 1957, 135, 263
[21] Hammond, P H *ibid* 1956, 132, 17P

Special Articles

HOTELS OR HOSPITALS?

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THERE can be no dispute concerning the national need for new hospitals. Conflict of view on what form they should take, and what function they should serve, may provoke original thought and avoid perpetuating unfortunate and costly errors. It would be flippant to suggest that the Government should build expensive hotels in which hundreds of thousands of citizens could live expensively but free (in so far as anything paid for by taxes is free) for such varying times as they or their doctors considered their health was below par. Unfortunately, however, there is a real danger that many of the millions pledged for hospital construction may provide hotels instead—and very expensive ones! The name "St. Trinian's Hospital" rather than "Hotel Sans Souci" in neon lights over the palatial entrance to a modern skyscraper will not alter the use made of its beds.

Intelligent planning and bold but reasoned experiment are necessary to build a hospital service worthy of the latter half of the 20th century and not a mere chromium-plated replica of a system now outmoded. A revolution in building and administration must be preceded by a revolution in thought. Most people find revolutions disturbing, but, in fairness to Governments that build and citizens who pay, a warning seems justified. To clamour for the spending of £750 million is foolish unless guidance is given on how it may best be spent. Wise planning and spending could result in Great Britain leading the world in a new concept of hospital service.

Great advances in medicine have transformed the legitimate demands that should be made on hospitals. Diagnosis is more rapid and accurate, and to an increasing extent is, or should be, an outpatient procedure, whereas previously it was not unusual for patients to occupy hospital beds for days and even weeks "under observation" while a diagnosis was made. (Although the justification now seldom exists, the practice is not entirely obsolete.) Treatment is now more precise. Where patients were once admitted with acute infections from which many died and others required long periods of intensive nursing, most are now treated effectively at home by the family practitioner. Developments in anæsthetic and surgical techniques have revolutionised surgery. The patient is no longer an invalid for weeks or months after a simple abdominal operation. He serves tea to his fellow patients a few days after a bowel resection or a lobectomy, and feels the better for it! Emphasis on positive health and rapid rehabilitation is increasing. The illness or the operation is an unfortunate interlude to be forgotten as soon as possible, and the whole hospital service should be so designed and maintained as to facilitate this process.

VALUE FOR MONEY

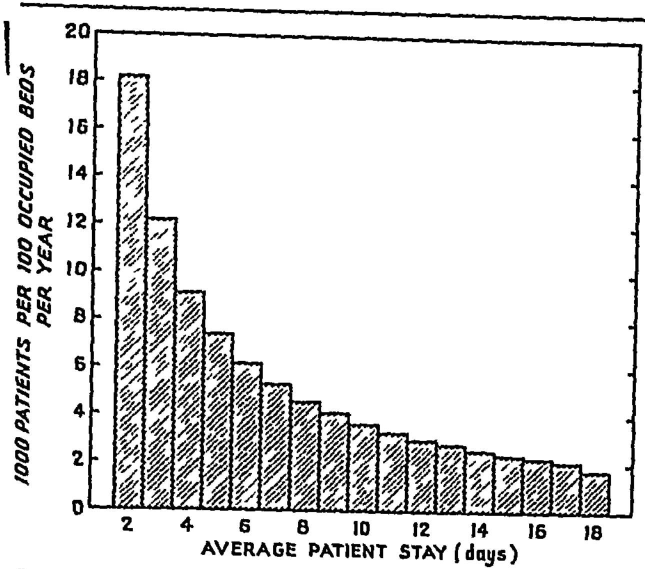
New techniques can demand highly specialised and expensive equipment and staff, and add to capital and maintenance charges. This is one excuse made for the high cost of the present hospital service, and will doubtless be used to justify greater expenditure in the future. The excuse is only partly valid. Accumulating evidence in published estimates suggests that it is widely accepted that hospital construction must be relatively expensive, even when special facilities and equipment are either not required or are minimal. For example the cost of new "acute" hospitals, planned or recently built, varies within a range of £3000 to £6000 a bed. Even the lower figure is nearly three times the estimated cost of accommodation per guest in new luxury hotels now being built in the London area. It is true that hospital charges expressed in this way include the cost of theatre suites, expensive equipment, nurses' accommodation, &c., but it is also true that with hotels the estimate provides for public rooms, ballrooms, restaurants, private bathrooms with every bedroom, and the other amenities considered essential in a modern hotel of international repute. This comparison is not to suggest that one is too expensive or the other surprisingly cheap, for only those with an intimate knowledge of all the factors associated with modern building could evaluate the two. It should however emphasise the great cost of a modern acute hospital and the relative expense of simpler institutions used in the hospital service.

If hundreds of millions sterling are to be spent on building, it is essential that the Government and the taxpayer receive value for the money. Expensive equipment should be used as far as possible solely for the purpose for which it was designed, and to the maximum of its capacity: industry achieves efficiency in this way. A surgical theatre suite makes its contribution to each patient in a relatively short time varying from minutes to hours. Too often, however, theatre and other expensive facilities are limited in the work they could do because beds are fully occupied. In the meantime waiting-lists grow with all the associated implications of disordered homes and absence from work. The generally accepted solution to the waiting-list problem appears to be "more beds." This would mean bigger hospitals, or more of them, with a corresponding increase in the cost of the hospital service. To adopt this policy would be short-sighted, for there are weighty arguments to support the view that a more efficient service could be provided with smaller acute hospitals and fewer beds. Factors already discussed are decreasing the demands made on certain sections of hospital beds at present available in fever and other hospitals. Many of these beds could now be used to advantage as suggested later.

STAY IN HOSPITAL

With these general concepts in mind, study of the Ministry of Health national costing returns for 1958 discloses some startling facts. Even the official definitions used are relevant. An "acute" hospital is one in which *not more than 15%* of the beds are "allocated to the excluded departments." This means set aside for the use of chronic sick and other categories of non-acute conditions. A "mainly acute hospital" can have *up to 40%* of its beds allocated to these purposes. This should be remembered when one considers the equipment, staff, and expense of a modern acute surgical or medical unit. To serve hot dogs at a shilling a time in the Savoy Grill would be uneconomic, and so is the established practice of keeping convalescent patients in acute hospital beds. What is urgently needed is a reappraisement of what is meant by a convalescent patient.

The 1958 report records that hospital A (a famous London teaching hospital of about 700 beds) had an average stay per patient of eighteen days. Hospital B (a teaching hospital of about 400 beds) had an average stay



Graph to correlate the number of patients who could be treated in 100 occupied beds with the average number of days they spend in hospital

of nine days There must inevitably be many factors other than the time patients are kept in hospital which differ in the two institutions, but they have this in common that both are general teaching hospitals with special departments, and both have reason to be jealous of the high standard of medical care provided The 700 beds in hospital A treated just under 14,000 inpatients in the year, while hospital B with 400 beds treated nearly 17,000 If hospital A reduced its average stay per patient to nine days it would double the number of patients treated to 28,000 If these patients were not available it could either close beds and reduce the size of staff, or admit from the waiting-lists of other hospitals working under greater pressure Furthermore, if hospital A were scheduled for rebuilding, it would be unrealistic to claim that it should be reconstructed as a 700-bed unit unless a reasonable case were made to justify this in terms of increased medical demands expected to be made upon its services

Conversely, if hospital B (average patient stay of nine days) decided for some reason it would work to a basis of an average stay of eighteen days, it would treat only 8500 inpatients instead of 17,000 as at present This would increase further its already huge waiting-list to such an extent that a public outcry (though misinformed) would almost certainly demand more beds and more staff To treat the same number of patients as at present, only with an eighteen-day average stay, it would need to double its size to 800 beds

This perhaps oversimplifies the position, but the available evidence in hospital and national reports confirms the basic truth of the argument No London teaching hospital in 1958 had an average stay of less than fourteen days and the range was up to twenty-four In the provincial teaching hospitals the range was nine to sixteen days The non-teaching acute hospitals of the Metropolitan area and the country as a whole had a corresponding variation in the average stay of patients An increase from ten days to twelve days per patient may seem small, but it represents a fall of about 15% in the contribution a hospital has been making and in terms of national figures it is of tremendous importance The chart demonstrates how the number of patients 100 occupied beds can handle in one year is related to the average length of stay

A low average figure is not in itself a goal to be aimed at, but it emphasises certain facts which are often overlooked The patient who stays in hospital a day longer than necessary *uses the hospital as a hotel* Major discrepancies between the average stay in hospitals of comparable size and purpose are a measure of the extent to which at the present time hospitals are used as hotels It is ironical that in many cases a patient could be more comfortable, have greater privacy, better food, and more quiet at approximately half the cost if he were in a hotel with several stars to its credit

Destructive criticism is easy, but a problem as vast and important as the National Hospital Service demands a constructive approach Any major reform is certain to challenge many traditional concepts and may arouse powerful opposition Experiment with pilot schemes can be valuable, for once facts prove a contention it is difficult for opposition to survive

BETWEEN HOSPITAL AND HOME

The phase of acute illness in medical and surgical diseases is now generally short A period follows of varying length during which there could be no better place in which to recover than at home under the supervision of the family practitioner, provided the necessary facilities exist and the patient and relatives desire it In America this early return home has been made necessary by the high cost to the patient of hospital care Hospital costs in Great Britain are also high, and are steadily increasing, but the Welfare State protects most patients from any personal financial strain when, with the acute episode safely over, they prolong their stay and convert the hospital into a hotel Unfortunately home conditions in Great Britain seldom warrant an early transfer, but with rising standards of living, better housing, and an effectively organised home-help service, it would be reasonable to expect improvements in the future

A major criticism of the present service is that little thought has been given to the problem of how to bridge the gap between the acute episode and the time when the patient could reasonably return home Early convalescence is usually spent in wards designed, equipped, and staffed for acute work In his excellent article on Hospitals for Today and Tomorrow[1] Farrer-Brown referred to a Nuffield Provincial Hospitals Trust survey team's findings that a quarter of the patients in medical beds in a general hospital could have been treated at home or in the outpatient department, and that nearly half remained in hospital longer than was necessary Those who need the facilities of an acute unit are kept waiting by those who do not

The solution is obvious Hospitals designed for acute work should be used for that purpose and *for that purpose only*, with early patient transfer to a simple, quieter, less expensive environment where medical and nursing requirements would be minimal Emphasis would be on self-help and rapid rehabilitation

Practical experience of this concept has revealed the advantage of the consultant responsible for the management of the acute phase of the disease retaining control in the convalescent annexe, but there is every reason to explore to an increasing degree cooperation with the family practitioner once patients have been transferred

The siting of these annexes could well vary according to local conditions Small towns can no longer have a modern and efficient hospital (This suggestion may be resented by some but it is an economic and medical fact)

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[1] Farrer-Brown, L. Brit med J 1959, i, suppl p 184

These towns, however, could be equipped with the new-purpose annexe and in this way allow their citizens to return among friends and relatives a few days after operation, or once the acute phase of illness was over This would help integrate general practitioners into the hospital service and facilitate continuity of care by the family doctor In the cities these convalescent annexes could be more closely associated with the acute hospital units, and, where space permitted adequate access to the open air and to gardens, it would probably be more economical to have them close to the acute unit In the meantime, however, use should be made of empty beds in fever hospitals and chest units

ADMINISTRATION AND NURSING

A 1000-bed hospital of the type now envisaged would differ from the present 1000-bed hospital in many ways, including nursing and administration Staffing of the acute unit would need to be generous, otherwise the strain would be too great. In the annexe, however, staffing would be minimal, and all possible use could be made of part-time workers The scheme suggested could help solve the nursing problem not only of Great Britain but of other countries as well It should also lead to a reassessment of the great expansion of hospital administrative personnel since the appointed day The Whitley Council system of paying certain staff on a points-per-bed (or cot) basis might be more efficient under the proposed scheme than under the present one

It may be argued that this plan would make nurse training harder If the responsible authorities wish to continue training nurses as at present, there would be weight in the criticism, but the changing face of medicine has modified the conventional pattern of nursing duties This fact is being too often overlooked, with the result that nurses spend time and energy in badly designed wards carrying unnecessary bedpans, wash bowls, and food dishes to patients who would be much better and much happier attending to their own needs if only facilities existed for them to do so In their hours of study nurses are trained in medical and surgical detail to an extent which would enable many to compete favourably in examination with medical students, and it is certain that this increased knowledge is not an essential to devoted, sympathetic, and skilful nursing (It can in fact be a handicap) In acute wards detailed nursing care is essential, but in the annexes the attention required would be slight Adequate rest and recreation rooms, ample bathroom and lavatory accommodation, cafeteria feeding, and modern kitchen and cleansing equipment, would reduce domestic staff to a minimum Conditions would be ideal for nurses from acute units to relax while acting merely in a supervisory capacity during spells off acute duty The psychological advantage to a patient of being transferred early from the hospital atmosphere of acute wards to the simpler and more relaxed life of the annexe would be considerable

WARD/ANNEXE BED RATIO

The ideal relation between the number of acute and annexe beds would vary from specialty to specialty and would require considerable preliminary experiment The greater the number of annexe beds in effective use the cheaper would be the hospital service From experience of practising these ideas at Oxford we believe that in gynæcology a reasonable relationship would be 30 annexe beds for an acute ward of 24 beds At no time have the convalescent facilities at Oxford been either adequate or sufficiently stable for a continued practical trial, and the ratio suggested may need adjustment after further experience Any alteration would probably be to increase the proportion of annexe beds

DEDUCTIONS FROM OXFORD EXPERIENCE

In the area department at Oxford 39 acute gynæcological beds accommodated 1991 surgical patients in 1958 and have averaged 1814 a year over the past five years 24 of these beds are at the Churchill Hospital and 15 at the Radcliffe Infirmary Because of shortage of convalescent beds the practice has been to give the Radcliffe priority over the Churchill in the use of beds available. The result has been that in 1958, with the same consultant staff, 925 operations were performed from the 15 Radcliffe beds, and 1066 from the 24 Churchill beds With an adequate senior staff and constant use of even the limited convalescent facilities used by the Radcliffe, the Churchill would have been able to operate on at least 1500 patients without being given any extra acute beds This would have reduced the gynæcological waiting-list from over 600 to practically zero within a year The next step would be to *reduce the number of acute beds*

Allowing an average stay of five days in the acute ward for major operative cases (many would require less) and ten in the annexe, a unit of 24 acute beds and 30 annexe beds should be able to treat 1500–2000 patients a year Those requiring special investigations would be admitted to the annexe in the first instance, be transferred the day before operation, and return a few days later For this volume of work the 24 acute beds would require theatre facilities for at least three major lists a week, preferably with two theatres available for each Daily access to a theatre, even if for only an hour, would enable minor cases and " day " cases to be handled in considerable numbers if a few beds were set aside for patients requiring minor procedures such as cystoscopies, pyelograms, and biopsies Even these demands would occupy less than half the available theatre time The remainder could be utilised by a comparable surgical unit handling approximately the same number of patients Thus a basic acute unit of two wards of 24 beds each, and a theatre suite of two theatres with a recovery room, should be able to treat surgically a minimum of 3000–4000 patients a year The size of the theatre suite would obviously be developed in proportion to the number of acute wards attached, but it will be apparent that a suite of four theatres serving four wards with a total of just under 100 acute beds could on the above figures treat 6000–8000 surgical patients a year This may well be an underestimate

To appreciate what this means in terms of present practice, these 100 acute surgical beds with their associated annexe facilities could treat annually at least as many surgical patients as the total of all patients at present admitted to some acute hospitals, teaching and non-teaching, of 300–350 beds A comparable reduction in the number of acute medical beds at present in use would seem reasonable The result would be acute hospitals of reduced size and improved efficiency, one indication of which would be the virtual abolition of long waiting-lists

In this concept of an acute hospital service we should need staff sufficient to use the facilities to full capacity, but there should be flexibility The idea of a consultant being given *x* beds on his appointment to a hospital and regarding these as his own for the remainder of his active life, to be increased possibly but never decreased, is outmoded and uneconomic It is hard to justify consultants (or teams of consultants) in any specialty retaining a considerable number of beds when they have almost no waiting-list, while the staff in another department struggle in vain against a constantly increasing pressure of work Admittedly the number of operations competently performed in a session is not the only index of a surgeon's contribution, but we can be pretty sure that two surgeons working as a team will do more than they could if they worked separately—and will do it with less effort Particularly is this so when the clinical load is heavy and when two theatres are used at one operating session When one consultant was away, or when pressure of waiting-lists required it, beds might be diverted temporarily from one service to another These are points which should be decided on grounds of need and common sense rather than privilege or pride

In the scheme here outlined an essential to success would be efficient teamwork by all concerned—doctors, nurses and administrators—determined to utilise to the full their resources By so doing they would render the greatest possible service to patients at the lowest possible cost

To explore the potential advantages, and also the difficulties both foreseen and unforeseen, a pilot trial would be necessary In terms of the projected £750 million building programme this would be inexpensive, but its results could be far-reaching

SUMMARY

Medical and surgical advances have changed the demands that can legitimately be made on hospitals They are not hotels

Hotels are cheaper than hospitals to build and maintain

A positive attitude to health should reduce to a minimum the time a patient spends in hospital

The acute episode of illness is usually short but its efficient hospital treatment is expensive

Acute beds should be used for acute work only, and should be integrated with relatively inexpensive annexes Estimates are given of the clinical potential of an acute surgical unit with annexe facilities

The acute hospital of tomorrow could be much smaller and more efficient than its present counterpart

An experimental pilot trial is advocated

NEW YEAR HONOURS

The list of honours published on Jan 1 contains the names of the following members of the medical profession

Baronet

Sir James Paterson Ross, K C V O, M S Lond, LL D Glasg, Hon F R A C S
President, Royal College of Surgeons of England, professor of surgery in the University of London at St Bartholomew's Hospital Medical School

K C M G

Lieut -Colonel Sir Charles Bickerton Blackburn, O B E, M D Sydney, F R C.P, F R A C P, R A A M C. retd
Chancellor of the University of Sydney

K C V O

Ivan Whiteside Magill, C V O, M B, D A Belf, F R C S

K B E

John Patrick Walsh, M B Melb, B D SC, F D S R C S
Dean, University of Otago Dental School

Knights Bachelor

Andrew Moynihan Claye, M D Leeds, Hon M D Melb, F R C S
President, Royal College of Obstetricians and Gynæcologists, professor of obstetrics and gynæcology, University of Leeds

Derrick Melville Dunlop, B A Oxon, M D, Edin, F R C.P, F R C.P E
Professor of therapeutics and clinical medicine, University of Edinburgh

Edward Ford, O B E, M D Melb, F R C.P, F R A.C.P
Director of the School of Public Health and Tropical Medicine, Commonwealth Department of Health, University of Sydney

William Wallace Stewart Johnston, C.B E, D S O, M C, E.D, M D Melb, F R A C P
Consulting physician, Royal Melbourne Hospital, for services to postgraduate education

C B (Military)

Surgeon Rear-Admiral Douglas Murdo Beaton, O B.E, L.R.C.P.E., Q H P

Major-General Frank McLean Richardson, D.S O, O B.E, M.D Edin, Q H S

Major-General Thomas Frederick Mackie Woods, O B E, M.D Dubl., Q H.P

C.M G

John Cairney, M D, F R A C S
Director-General and Inspector-General of Hospitals in New Zealand

C B E (Military)

Air Commodore William Percivale Stamm, M B Lond, F.R.C.P, Q H S, R A F

C B E (Civil)

Stanley Alstead, M D Lpool, F R C P, F R C P E, F R F P.S
Regius professor of materia medica and therapeutics, University of Glasgow

Louis Abel Célestin, M C, M D Lond
For public services in Mauritius

Thomas Frank Davey, O B E, M D Manc
Senior specialist (leprologist), Eastern Region, Nigeria

George Lightbody Montgomery, T D, M D Glasg, PH D, F R.C.P E
Chairman, Scottish Health Services Council, professor of pathology, University of Edinburgh

Timothy Joseph O'Leary, M B N U I
Senior flying doctor in Queensland, Royal Flying Doctor Service of Australia

Robert Wilfred Scarff, M B Lond, F R C S
Professor of pathology in the University of London at Middlesex Hospital Medical School

Leonard Anthony Paul Slinger, O B E, M B Cantab
Director of medical services, British Guiana

Dorothy Mary Taylor, M D Edin, D P H
Senior medical officer, Ministry of Health

O B E (Military)

Lieut -Colonel Thomas Welsh Carrick, M B Glasg, R.A M C.

Colonel Richard Geoffrey Champion de Crespigny, E D, M B Melb, F R A C P, R A A M C

Surgeon Commander Joel Glass, L R C P E, R N

O B.E. (Civil)

Alfred Bimbisara Abayomi-Cole, M B Durh
Senior medical officer, Sierra Leone

Robert Calderwood, M B Glasg
Lately deputy secretary, Ministry of Health, and deputy director of medical services, Singapore

Stanley Walker Cooper, F R C S E
Surgical specialist, Ghana Medical Service

William Alexander Cramond, M D Aberd
Physician-superintendent, Woodilee Mental Hospital, Lenzie

John Ralph Donaldson, E D, M B Melb
Formerly commissioner, St John Ambulance Brigade, Western Australia

William Glyn Evans, M B Wales
Lately director of medical services, Sarawak

Soyode Obafunmilayo Olumuyiwa Franklin, M B Dubl
Chief medical officer, Ministry of Health and Social Welfare, Western Region, Nigeria

Jean Arthur Gemmell, M B Edin
Medical superintendent, maternity clinic, Aden

Charles Henry Gurd, M D Brist
Physician-specialist, Fiji

Alan Waites Hansell, M B Lond
General practitioner and medical officer of health, Bedale, Yorkshire

Ian William James McAdam, M B Edin, F R C.S E
Professor of surgery, University College of East Africa, Makerere

Duncan Macmillan, M D Edin, F R C.P E
Physician-superintendent, Mapperley Hospital, Nottingham

John Alexander McVicker, M B Belf
Member, Northern Ireland General Health Services Board

Elizabeth Theodora Mess, M B Lond, F R.C S E
For public services in the Northern Region, Nigeria

Alberto Maria Rodrigues, M B E, E D, M B Hong Kong
For public services in Hong Kong

David Scott, M D Camb
Specialist epidemiologist, Ghana Medical Service

Eileen Rosamund Barter Snow, M B Lond
Principal, Christian Medical College, Ludhiana

Douglas Eric Thompson, M B Camb
Senior medical officer, Tanganyika

HUGH BRYSON CALWELL WALLACE, M D Belf
Specialist physician, Malayan Medical Service
MAURICE HOLLAND WEBSTER, M B Aberd
Director of medical services, Northern Rhodesia, for his work in providing a health service during the construction of the Kariba Dam
BASIL DUDLEY WHITWORTH, M B Camb
Director of medical services, Swaziland

M B.E (Military)

Major DOUGLAS STUART PATON, M B Brist , R.A M C.

M.B.E. (Civil)

JAMIETRAM KRISHNARAM DAVE, L.C.P S
For public services in Tanganyika.
FRANCES MARY HANCOX
Medical missionary in Colombia
WALTER PARKER HARRISON, M R C S
Member, National Service medical board, Lincoln
WILLIAM ALFRED CONRAD HORTOR, M.R.C.S
For public services in Jamaica
ADAM SOLTYSIK, M D Lwow
Surgeon specialist, Grenada, Windward Islands
HENRY THOMPSON STRUDWICK
Medical officer, Jamaica

Occasional Book

GÖDEL'S PROOF

IN these days of automation, mechanical translation, and computer-made election forecasts we find mathematics everywhere pervading daily life We are almost approaching the point where it will be the man who fears mathematics, rather than the absent-minded mathematician, who is unfitted to deal with his environment It is therefore consoling to hear of a mathematician who can prove that the foundations of the forbidding edifice of reason erected by men such as Bertrand Russell are little more secure than those supporting the ramshackle huts of commonsense which most of us inhabit

Two American mathematicians, Ernest Nagel and James R Newman,[1] have lately set out to bring before a wider public the Incompleteness Theorem in which Godel shows that mathematics contains an inevitable loophole, which may be looked upon either as a fatal defect or else as a vital element of flexibility which saves it from ultimate sterility, depending on the point of view

Kurt Gödel was born a Czech in 1906 and showed the usual early interest in mathematics In 1924 he moved to Vienna, there reaching a post equivalent to that of assistant professor in 1933 By then his interests included the philosophical implications of mathematics and it was in 1932 that he made his most individual contribution, by proving, in his own phrase, the " inexhaustibility " of mathematics and publishing his theorem. In 1938 he emigrated to America to work at the Institute of Advanced Studies in Princeton, where he came under Einstein's influence and much of his later work has been concerned with relativity In 1951 he was co-recipient of an Einstein award.

The proof of his theorem requires the use of a code according to which every possible mathematical statement, argument, symbol, or proof can be translated into terms of a new language A translation of this kind is loosely similar to translating (say) English into French, but just as a mathematical language or " calculus " is more exact and unambiguous than any ordinary verbal language, so also a mathematical translation or " mapping " is more rigorous and formal than an ordinary linguistic translation

We may describe a Gödel mapping as a coding procedure capable of converting a page of mathematical argument into a sequence of entirely numerical formulæ For example, the identity 0=0 becomes the Gödel Number $2^6 3^5 5^6$ (i e., 243,000,000) according to the rules of the procedure, and any other sequence of basic mathematical-logical symbols can similarly be represented by a unique Gödel Number Any Gödel Number can be broken down into its factors in order to arrive at the original mathematical-logical sequence which it represents and as a result of the rigid correspondence between the two parallel languages, the arithmetical relationships existing between different Gödel Numbers stand for relationships between the equivalent statements in ordinary mathematical logic. In other words, statements about Gödel Numbers are statements about mathematical logic (as distinct from statements *within*, or expressed in, mathematical logic) Furthermore the coding-rules devised by Gödel are such that the ordinary laws of arithmetic apply to Gödel Numbers—they may be multiplied, divided, factorised, and so on, as if they were ordinary numbers with no special meaning It follows not only that arithmetical manipulations of Gödel Numbers are possible and that they are logical statements about logic, but also that the logic in which these statements are made is similar to the logic about which they are made

When a language (composed of words or symbols of any other kind) is used in order to discuss some other language, such discussions are said to be carried on in a " meta-language " Statements about mathematical logic are therefore called " metamathematical ", no matter what terms they are couched in, because mathematical logic constitutes a language, and metamathematical assertions, as we have seen, can be expressed as more or less simple calculations with Godel Numbers Since the rules of these calculations are identical with the rules of the original mathematical calculus under discussion, it is clear that in this case the rigour of the meta-language is no greater and no less than that of mathematics itself

Now it is obvious that mathematics cannot possibly be wholly translatable into another set of symbols (such as the Godel Numbers) until it is itself expressible in a finite number of symbols One cannot make a strict translation from French into English of ideas which a Frenchman cannot accurately express in French The attempt to make mathematics formally and fully expressible has been undertaken by various authors, Bertrand Russell among them, and it is what mathematicians mean by the axiomatic method

The axioms are the basic unproved assumptions of the system They are expressed in symbolic form as a set of statements and the symbols are of two types—variables and connecting-signs The meaning of the axioms resides in the fact that the variables are only allowed to be connected in strictly specified ways—the axioms are in fact the exposition of the ways in which the variables and connecting-signs may be combined, reduced to the simplest terms In addition to the axioms other " formulæ " can be made up from the same symbols Formulæ are the formal symbolic equivalent of sentences in ordinary language and the progression from one step of an argument to the next depends on altering the first formula (or sentence) into the next, or combining two formulæ already derived, to produce a third Strict rules define the permissible ways of making these combinations and substitutions

A little thought will show that the axioms and the transformation rules together make up the arbitrarily established rational basis of the entire system and are, in short, its " dogma " The symbols serve only as tokens to be manipulated in obedience to the restrictions of this dogma The axioms of a formal system must all be tautologous—that is to say that the structure of these statements is such that they remain valid irrespective of their content For example, the algebraic identity $(a-b)(a-b)=a^2-b^2$ is a tautology and it can be verified by substituting for " a " and " b " any numbers we choose. In the same way, the logical axiom (pVq) ⊃ (qVp) is tautologous and conveys the same logical attitude about alternative possibilities, whatever phrases or sentences may be substituted for p and q Furthermore, the transformation rules are such that every formula derived from the axioms by their application must also be a tautology, such formulæ are called theorems On the *other hand*, it must also be possible to combine the symbols of the system in such a way that a formula results which is not tautologous, is not derivable *from* the axioms via the rules, and is therefore not a theorem Oddly enough at first sight, this last is a necessary condition *if the* axiomatic system is to be consistent, for the following reason

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[1] Nagel, E , Newman, J R Godel s Proof London Routledge & Kegan Paul. 1959 Pp 112. 12*s* 6*d*

By " consistency " is meant that the dogma of the system is such *that it is* impossible to derive from it both a proposition and its formal contradiction, this is *obviously* an indispensable condition of rational thought It can be shown that if both the proposition and its negation can be derived in a single instance, *the same can be done for all propositions*, therefore, any *proposition whatever can be proved* and the system is valueless Conversely, however, if it can be shown by *metamathematical* argument that there is a single proposition which cannot be proved, it follows that the system is consistent and rational *To prove a system consistent*, all that is needed is to discover a single formula which can be shown *not* to be demonstrable *from the axioms* via the rules and is therefore not a theorem To prove in addition that a formalised system is *complete* requires a metamathematical demonstration that every true statement expressible in terms of the symbols of the system must also be capable of step-by-step derivation from the axioms

What Godel did was to construct the Gödel Number corresponding to a certain formula, this formula being expressed in what purported to be a complete and consistent axiomatic calculus He also constructed the Number for the negation of this formula Clearly, one or the other of these numbers must represent a true statement Now, the formula in question was the metamathematical statement that *the formula itself could not be derived* from the axioms via the rules Thus, either the formula (and the statement) are true, in which case the formula cannot be proved, or else the *negation* of the formula must be true, in which event the statement must be false and the formula therefore demonstrable although false Consequently mathematics must either be incomplete or inconsistent, for (when strictly coded into *Godel's meta-language*) it permits of the construction of this paradoxical formula

By similar methods Godel showed that it was possible to construct a Godel Number corresponding to the assertion " The calculus is consistent "—i e , " There is *at least one formula in the calculus which is not demonstrable* "—and then to show that this assertion was not itself demonstrable by the arithmetical manipulation of Godel Numbers The importance of this proof is that arithmetical reasoning is shown to be insufficiently powerful to demonstrate its own consistency; the possibility is, however, left open that the consistency of mathematics might be demonstrable in terms of a non-mathematical meta-language

There is an interesting psychological application of the second of these two proofs When the attempt is made to prove the absolute consistency of a formal calculus in terms of a meta-language which obeys the same dogma as the calculus itself, the situation is similar to that of a man who attempts to calibrate one *instrument*, such as a ruler, against another from the same factory The best that can be hoped is that the measurements made by the two instruments will lend each other support, for, when they disagree, neither can claim the final authority If we accept that human reason is incapable of achieving a watertight proof of its own rationality, even in the strict language of formal logic, the same must apply still more forcibly to reasoning carried on in the *far less precise and* stable language which we ordinarily use, unless we relinquish the hypercritical standards of absolute proof which logicians demand The critical evaluation of one's own reasoning, in short, is probably quite as fallible as the reasoning itself, and " second thoughts " no more reliable than " first impressions "

If it is correct to argue from the particular case of mathematics in this way, then when a man analyses a possible flaw in his own thinking, he is indulging in what might be called " meta-thinking " and the result is liable to be a deadlock unless either he is prepared to be content with something less than certainty, or he is capable of greater rigour in his meta-thinking than in his suspect *first thoughts* We know that this type of deadlock can occur and may reach pathological dimensions, the perfectionist is very prone to lapse into obsessional doubt, to demand absolute certainty and to ruminate ceaselessly on one topic or another It is perhaps also relevant that one symptom of the severe anxiety to which obsessionalism can lead is the fear that reason may be completely lost The analogy with " inconsistency " needs no underlining

From a therapeutic standpoint these considerations suggest that such people may be helped, in general, by whatever gives them the confidence to accept a degree of uncertainty—whether this agent be a pharmacological euphoriant or some kind of reassuring relationship Indeed, we do find that obsessional people *tend to seek* a father-figure Another approach should *theoretically* be the introduction of a fresh meta-language, capable of greater rigour than either the first thoughts or the critical second thoughts of the patient, in other words, someone who will do his meta-thinking for him This interlocutor would have to be of higher *intellectual discrimination* than the patient and free from the particular pre-occupation which besets him, he would then be in a position to redefine the problem and to throw his weight on one side or the other

In practice the *necessary* " third language " is often provided by an established source of formal dogma covering the main area of conflict, whether it be religion, politics, sex, or some narrower topic A dogma relieves the victim of any need to decide and may liberate his mind for other pursuits, but for this recourse to be available to the patient the source of dogma must be acceptable It may be that the occasional effectiveness of analytical psychotherapy in relieving what are, in effect, deeply buried obsessional pre-occupations (" conflicts ') depends upon a combination of two simultaneous processes—on the one hand the gradual eliciting of material and the analytical breakdown of the patient's problems to a few central issues, and on the other, the cultivation of a transference relationship which *establishes* the analyst as an acceptable source of dogma on these issues

The psychological analogy with Godel's work provides a crumb of comfort for those who occasionally doubt their own sanity It will be remembered that in the first of his proofs, the alternative to mathematics being irrational and inconsistent was that it must be incomplete Godel himself regarded this second alternative as meaning that mathematics was an inexhaustible field for *empirical* discovery, and it is *consoling*, surely, to feel that one can interpret one's state of mind at such times either as insanity or as intellectual fecundity

In England Now

A Running Commentary by Peripatetic Correspondents

As I approached the group of five-year-olds, I could see that they were in a state of anxiety and excitement. One of them, Samuel, was near to tears At their side Samuel's large dog was happily eating my sandwich lunch "Quickly, quickly," cried a little girl, "the dog is eating your sandwiches" And Samuel added his plea, "Hurry up, Mister, white bread is bad for him."

* * *

I have lately received a number of inquiries which show that in these days of crowded resorts and high fares the hospital holiday is becoming increasingly popular Many people, I know, look with disfavour on surgical operations, though in my opinion this is generally based either on misconceptions or on deliberate misrepresentation by selfish addicts who fear to see their own pet preserves invaded. I myself have always found a visit to one of our justly famous hospitals a very pleasant change

Last year I hesitated for some time between a festival of modern music, an undoubtedly attractive tour organised by a botanic garden expert, and one of the big peace marches, but recalling the delights of previous experiments in this somewhat lesser-known field—the nurses, the flowers, the grapes, the hours of leisurely reading—I found myself once again unable to resist the call of the clinic.

Here let me sound a note of warning Just to decide upon any operation, without paying due attention to the enchanting alternatives offered, is equivalent to saying "I'll go to Italy" instead of "I'll go to Cannobio or Torri del Benaco" And I am sure I shall hurt no surgeon's feelings—and it is my considered opinion that no body of men has done more for the tired business man than our surgeons—when I remind readers that, just as there are hospitals and hospitals, what may be suitable for one man may prove disappointing to another Indeed, there are as many fascinating facets to the relinquishment of superfluous parts of the human body as there are lakes in Italy and Switzerland, or forms of Roman or Florentine architecture I heard, for example, of a chartered accountant who, wanting just a short break from an arduous but lucrative practice, made the mistake of choosing an incision instead of an excision His disappointment was intense, and he returned to his office feeling little better for the change True, the holiday was not a total loss there was the initial anæsthetic—that delightful moment equivalent to the first trembling of the boat beneath one's feet or the sight of the trees falling away as the plane takes off—but the exhilaration of awakening from deep sleep to find that yet another unwanted oddment of the body had been sloughed off was lacking

The wise man will select his hospital as carefully as his operation, and here let me say that it is no longer necessary to confine oneself to the better-known resorts The large and fashionable establishments such as Guy's and Barts naturally offer a wider range of exciting and even novel possibilities, and are, of course, famous for their varied choice of anæsthetics, but many smaller and less-known hospitals cater for the discerning visitor who prefers to go somewhere more off the beaten track, and at a price to suit even the slenderest purse I know of one small and unpretentious establishment within twenty miles of London which will do an all-in appendectomy for very little more than the cost of a visit to Glyndebourne.

Few who have not experienced this type of rest cure can realise to the full the amenities of hospital life At what hotel, for example, are *all* meals served in the bedroom without extra charge? At what hotel will the chambermaids uncomplainingly make your bed while you are still lying in it? At what hotel will that same bed be moved in fine weather on to an airy balcony, or two creamy arms raise you carefully on your pillow when you wish to read and lower you as tenderly back when you wish to sleep?

I fear I may be taken to task if I fail to point out that many hospitals are as yet unlicensed, though an occasional glass of brandy can, I am told, be obtained by those who know the ropes In my opinion, however, this point is of less importance than might at first appear I have already referred to the variety of anæsthetics available to guests in most of our hospitals, and a wide choice of out-of-the-way beverages is to be found in the cellars of the more select houses, and I have yet to meet the connoisseur of fine drinking who, once he has discovered the fascinating bouquet and colour of some of the really great prophylactics, will willingly revert to his former tastes

One last word of warning Though hospital holidays are not yet fully commercialised, more and more people possessed of the pioneering spirit are becoming aware of their possibilities, so that already a certain amount of advance organisation is necessary Inquiries can be addressed, through your own local agent, to any reputable specialist

* * *

When I start to do a barium meal I usually like to get some grasp of the patient's complaint with the help of a few opening questions about gastrointestinal symptoms The replies are varied, often irrelevant, and often at variance with the history which has been elicited by another consultant in the outpatient department, though not necessarily on that account any less accurate Perhaps the most unkind reply, however, was "I have had everything wrong that my doctor can think of, so he sent me along here for an X-ray"

* * *

It is all very well to bemoan the pædiatrician's burden at Christmas, but has anyone given a thought to the burden of the psychiatrist in a mental hospital?

It was the Medical Superintendent's idea "All part of the open-ward policy," he explained. "Father Christmas means freedom for millions A visit from him, more than anything else, will show our chronic patients that they're free to come and go as they please. And you, Smith," he paused and looked at me, "will be Father Christmas"

On the day I was dressed up, given a large gin and, to the accompaniment of raucous cheers from people I had hitherto regarded as friends, started my round At the first ward the patients were all gathered in the entrance hall None of them took the slightest notice of me, despite the nurses' attempts to stir up excitement. I left quickly for the next ward, my spirits rising as I calculated that I ought to be back in the mess in a quarter of an hour This shows how fatal it is to make predictions, for in the next ward I met someone who really was Father Christmas He was seething with rage at the idea of being impersonated He told me that he was the one and only Father Christmas and that I was almost everything under the sun except Father Christmas I was so alarmed that I stepped backwards and, tripping over my gown, fell on my back. For one dreadful moment I lay helpless Then I had one of those rare moments of inspiration. "Your Majesty," I babbled from beneath my beard, "I am not Father Christmas In fact I have come especially to find and escort you round the hospital The reindeer have been delayed, but we can walk. . ." It was four hours later before I got back to the mess

Father Christmas is a changed man and the Medical Superintendent hopes to discharge him home shortly As for me, I'm thinking of emigrating to one of the less progressive countries before next Christmas

* * *

The other day I used the word "carminative" and was promptly asked by a member of my family whether I was referring to one of the B M.C. new baby cars

* * *

OATS AND CIRCUSES

Mokerleatotes
Givvimum inbag
Scotterleatotes
Givvimum indish
Anybody mustavvizotes
Givvussor larotes
Wile dotes anantidotes
Forplentiotes
We votes

Letters to the Editor

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—Having for some years made a practice of carefully observing infantile cavernous hæmangiomas, and having rarely undertaken any early treatment for these lesions during this period, I am surprised at Mr Denis Browne's strictures on Dr Simpson's article (Dec 12) It is my practice to explain to the mother the facts about the natural resolution of the majority of cavernous lesions, if necessary to show her photographs of cases in which this has occurred, and to ask for her cooperation in regular observation of the baby In my experience the mothers are happy to follow this course, and on only one occasion has a baby subsequently been taken elsewhere (in this case to a radiotherapist who treated the lesion) I have found that, despite early enlargement of some of these hæmangiomas during the first six months, the ultimate results have generally been most satisfactory Residual lesions can be excised if necessary but it is unusual for the final condition to warrant this

Dr Jones states that statistics can be misleading and that large numbers must be studied It is a common fallacy that "large numbers" add to the validity of observations whereas the careful observation of small numbers of strictly comparable cases is often far more rewarding The figures quoted by Dr Jones are certainly rather confusing Thus, at the Presbyterian Center, New York, it is stated that 135 out of 584 patients with cavernous hæmangiomas were untreated, and Dr Jones seeks to compare these with Dr Simpson's 170 lesions of which 140 were untreated I would submit that it is unwise to attempt to compare the two series However, if one is seeking information about the natural history, Dr Simpson's series (in which 82% of lesions were not treated) should be more informative than the American series in which only 23% of patients were untreated Dr Jones includes reference to 329 patients with hæmangioma simplex in the American series, but Dr Simpson's paper was not concerned with this type of case

Dr Jones goes on to refer to 814 out of 1752 "angiomas" (were these all cavernous?) which received X-ray therapy in Sussex and Kent He states the criterion of recovery but gives no information about the results achieved, or when the improvement occurred It is implied that a number of cases had repeated treatment and it is plain that almost 25% were still being treated after a five-year period Dr Jones also states that only 20% cleaned in the first year I must confess that I find it impossible to gain any precise idea of the Kent and Sussex results referred to by Dr Jones though I gather that he regards the cosmetic result as better in the treated cases

I have read Dr Simpson's paper with care and, as a surgeon, I find little with which I disagree In his discussion he makes it perfectly plain that residual lesions can be better treated at a later date, but his brief summary gives a slightly misleading impression of his views in that it baldly concludes "no treatment is necessary"

London, W 1 REGINALD S MURLEY

LEAF PROTEIN AS HUMAN FOOD

SIR,—It would be superfluous to say that Mr Pirie's proposals for the use of leaf protein as human food (Nov 28) are highly commendable and deserve success but there are blemishes in his argument that should be removed

He stated that "it is likely that a deficiency of any aminoacid in one protein (in leaf) will be compensated for by the other proteins, so that there will be no extensive deficiencies or excesses in the mixture" Likely perhaps, but, unfortunately, not true

Cabbage protein[1] contains less than 50% of the isoleucine, leucine, S aminoacids (i e, methionine+cystine), phenylalanine, and valine of egg protein, which can be regarded as the standard Kale contains less than 50% of the isoleucine, lysine, and S aminoacids, mustard greens less than 50% of the threonine, isoleucine, leucine, S aminoacids, and phenylalanine, sprouts less than 50% of the isoleucine and leucine of the egg standard These analyses are supported by biological estimations on cabbage protein[2] and two fractions of grass protein[3]

The primary requirement of a protein supplement for human feeding is a high content of methionine and cystine as most human diets are limited by this pair of aminoacids[4] Leaf proteins make no major contribution to this demand The isolated proteins of lucerne[5] contain 50% of the methionine+cystine of egg, 60–70% clover, 55% groundnut leaves, 50% barley grass protein

The experiment on pigs quoted by Mr Pirie, showing that leaf protein was as good as fish meal, was supplementation of a cereal ration in which lysine, not methionine, was limiting Further, the level of protein fed was too high to reveal possible differences between leaf protein and the fish-meal control (Moreover, fish meals can range from poor to good as proteins go)

These limitations are set out not to abolish but merely to reduce the height of the hopes set on leaf protein

This said, there remains the enormous problem of presentation Mr Pirie speaks of British prejudice to the green colour, but prejudices are worldwide and difficult to overcome In Guatemala the protein intake has been substantially increased in an acceptable way by adding cottonseed-maize to the local gruel This procedure is not acceptable across the border, because the supplement imparts a slight colour to the food This would suggest that no efforts should be wasted in offering leaf protein to verdophobes but only to such areas where the colour is considered advantageous

What is needed is a good cook/chemist/home-economist to produce an edible finished product that suits local custom and thus becomes acceptable

Bovril, Limited,
London, E C 1 A E BENDER

SIR,—Mr Pirie's reply (Dec 26) to the letters of Dr Cicely Williams and Mr Allen deals effectively with their criticism, and clarifies a number of the details mentioned in his original article The problem of getting enough food is a desperately serious one to millions of people, and it is encouraging to see basic research directed towards its solution There are a couple of points which have been raised in the present discussion which seem to me to merit amplification

The first is the question of the nutritional value of leaf protein Mr Pirie states that for pigs, chickens, and rats the protein extracted (from English leaves) is as good as, or a little better than, fish meal, "though not as good as the pre-eminent proteins—casein and egg albumin" If this is found also to be true for human children and tropical leaves, it will be good news for those areas where there is a deficiency of total protein

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1 Amino-acid Content of Foods Home Economics Research Report no 4, U S Department of Agriculture
2 Bender, A E, Miller D S Unpublished data
3 Davies, M, Evans, W C, Parr, W H Biochem J 1952, 52, xxiii
4 Miller, D S, Dema, I S Proc Nutr Soc 1958, 17, i
5 Proteins in Foods Indian Council of Medical Research, 1953

in the diet. However there are many areas where the dietary intake of protein appears to be adequate but signs of protein deficiency still abound, and it is found that the protein is almost exclusively of vegetable origin. In Uganda for instance, there is an impressive amount of kwashiorkor, and of the milder form manifested by retardation in growth, but recent experience with distribution of skim milk powder[1] showed that even those children who received a relatively small amount (well below the amount currently recommended by UNICEF) showed a substantial improvement in weight gain. The proceedings of the Third Inter-African Conference on Nutrition[2] bear witness to the need for further investigation of the nutritional status of groups consuming different proportions of foods of animal and vegetable origin, and this was emphasised in the recommendations of the conference. In her admiration for Samuel Smiles, Dr Cicely Williams may be contemptuous of "the teaching propounded by foreigners, who have spent most of their time concentrating on the virtues of skimmed milk", but virtues cannot be lightly ignored, even if propounded by foreigners Self-sufficiency, particularly in the production of foodstuffs, may seem elementary good sense, but I have the impression that economists are all in favour of trade, and there appears to be plenty of scope for trade in skim milk powder—if only the powers-that-be would develop it.

The other point, a small one, springs from Mr Pirie's observation that there is room for improvement in the varieties of vegetables grown in the tropics Indeed there is, and for passing on the knowledge to local farmers At present, economic interests being what they are, tropical plant breeders are occupied almost exclusively with improving cash crops—cocoa, cotton, coffee, &c.—and with making these available to farmers Even where better varieties of food crops have been bred (as with maize at the Cotton Research Station in Uganda) no effort is made to encourage their use by farmers Here again there is scope for action by the powers-that-be.

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JOHN McFIE

SIR,—Are not Mr Pirie (Dec. 26) and Mr Allen (Dec 12) both partially correct? Of the nutritive value of leaf-protein there would appear to be no doubt, but as a processed food for human consumption would there not be many difficulties?

The essential reason for malnutrition, certainly as one saw it in the 1930s in Southern Nigeria, was poverty The same period coincided with the effects of a world economic slump which led to a prolonged and catastrophic fall in local produce prices

While recognising that certain basic dietaries in parts of Nigeria are much more vulnerable than others, one must appreciate that millions of Africans live a normal healthy life, supplementing their own dietary Any new food concentrate would have to have a very special appeal and be available to those most needing it without extra cost.

Actually the introduction of what is essentially a protein supplement would not be new to Nigeria. I understand that attempts are now being made to popularise 'Food Yeast.' My own experience was with 'Marmite', and the demand for it later became so great as to far exceed its therapeutic use. Its success depended on (1) as a therapeutic agent it was dispensed free, (2) it had a visible effect on what was then a very prevalent condition, (3) its palatability appealed to those otherwise dependent on a predominantly vegetarian diet, and (4) it did not offend dietary custom or habit.

I also used a large amount of dried brewer's yeast. Though effective therapeutically, its taste made it unpopular

I doubt whether a protein leaf concentrate would achieve any direct objective On the other hand, provided costs permit, it could be supplied to animals and thereby be an indirect source of food.

Parkstone Dorset

D FITZGERALD MOORE.

TREATMENT OF BLEEDING PEPTIC ULCER

SIR,—Blind gastrectomy has saved and will save many patients who would otherwise die of hæmorrhage. We must stop the bleeding without exhausting the patient's reserves By all means let us try any promising method, such as that quoted by Mr Downie (Dec. 12) But once it is clear that operation is necessary a determined policy must be pursued This means rapid replacement of blood, and operation within two hours of the decision to operate.

When the abdomen has been opened the following rules will help young surgeons who have to do the bulk of this work.

(1) Exclude portal hypertension.

(2) Rapidly examine the upper jejunum for contained blood. If present, bleeding is active and there is need for haste If absent examine the ileum. Blood within often means that bleeding from the upper alimentary tract has temporarily ceased and there is more time for search.

(3) Inspect and palpate the proximal duodenum and the whole of the stomach. The left hand is the more useful. Open the lesser sac with the forefinger and middle fingers above the stomach and palpate the back of the stomach. An irregular fatty patch with irregular vessels near the lesser curvature on either surface indicates an ulcer If the stomach contains much blood, open it at once. Remove clots manually and fluid with the sucker (Twice in one week I found large holes in the splenic artery from ulceration on the back wall of the stomach far to the left.)

(4) If no obvious source of bleeding is found re-examine more thoroughly the whole of the small bowel looking especially for such lesions as the hæmangiomata described by Mr Lytton (Dec. 26) and Mr Read (Jan. 2), or an ulcer in a diverticulum

(5) If no bleeding point or ulcer has been found do not make further search in the stomach but do a two-thirds Polya gastrectomy In the course of this the bleeding point may become obvious, as for instance a small ulcer on the postero-inner wall of the duodenum. The crater may be seen in the open duodenal stump or the artery (usually a short branch of the anterior pancreatico-duodenal) may be seen spurting while the duodenum is being cleared.

After operation examine the excised stomach, slitting up the greater curvature. The bleeding point may sometimes be found on holding the specimen up against the light. Mark any suspected area with a black silk stitch as a guide to the pathologist.

With such a policy a few stomachs will be needlessly sacrificed but many lives will be saved.

Edgbaston,
Birmingham.

FAUSET WELSH.

SIR,—The discussion provoked by the two articles on hæmatemesis (Dec. 5) raises the important issue of selection of patients for operative arrest of the bleeding There is little doubt that a policy of selective surgery is effective in lowering the mortality from hæmorrhage provided that an early decision is reached in suitable cases Early identification of the lesion responsible for bleeding is of great importance in this connection so that patients with recurrent hæmorrhage from chronic peptic ulcers can be operated upon without delay

At the Central Middlesex Hospital we have attempted to meet the need of early ætiological diagnosis by a combined procedure of immediate gastric aspiration (for pH analysis) followed the morning after admission by gastroscopy and shortly thereafter by barium-meal examination done on the ward using a portable X-ray apparatus. Of the last 150 admissions for hæmatemesis correct diagnosis has been achieved in 80%, by this method, usually within 36 hours of admission. The possession of information of diagnostic value as to the cause of illness in circumstances of recurrent bleeding greatly assists the often difficult choice between operative and conservative treatment Indeed, in the last week during a surge of peptic activity in north-west London, 6 patients have undergone emergency gastrectomy for bleeding in this hospital, and in all but 1 patient, whose restlessness prohibited investigation, the decision to operate was undertaken with foreknowledge of the responsible lesion 4 of these patients were bleeding from chronic gastric ulcers, a group in whom surgical treatment is particularly indicated

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[1] Welbourn H F Lancet, 1959, i 1248
[2] Proceedings of 3rd C.C.T.A. Inter-African Conference on Nutrition Angola, 1956

The importance of reaching an early decision between surgical and medical treatment of bleeding peptic ulcer cannot be overemphasised, for rapid deterioration despite apparently adequate replacement of blood by transfusion is common and delay in seeking surgical aid too often fatal It is our experience that the procedure of early investigation is both informative and harmless and is an important factor in the successful management of patients bleeding from an unknown lesion in the gastrointestinal tract

Though full investigation by pH analysis, gastroscopy, and early X-ray examination may be impracticable in most hospitals, we have found that ward barium-meal examination using the portable X-ray machine gives diagnostic information in more than three-quarters of patients admitted after hæmatemesis This simple radiological procedure is well within the scope of a general hospital The detailed technique will shortly be published

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G N CHANDLER

POSTCOITAL EXAMINATION OF SEMEN

SIR,—For the past twelve years I have, with few exceptions, referred all husbands of my infertile couples to Dr Davidson (Jan 2)—several hundred of his 12,000 cases From my personal experience I can say that Dr Davidson's direct semen examination has "saved many women a great deal of unnecessary investigation, discomfort and eventual frustration" The majority of subfertile men can be improved

I can endorse everything Dr Davidson has said in his letter

Croydon

ARTHUR CLIFT

DENTISTS AND ANCILLARIES

SIR,—I must point out that Mr Markham (Dec 5) failed to stress the fact that insufficiently trained persons will be practising on the youth of this country if dental ancillaries are in being

Your remarks about the apparently unattractive nature of the work of a dentist seem contrary to the fact that some hundreds of applicants all over the country are being turned away annually by the dental schools In the House of Commons, Mr Walker-Smith admitted "As a matter of fact there is no shortage of recruits to the dental profession at the present time" He did not think inducement grants were needed "It is really a matter of accommodation, and we are getting on as fast as possible"

Surely the public, and in particular the children, are entitled to dental treatment by fully trained and qualified dental surgeons 38 years after the 1921 Act we still see the results of unskilled treatment, and while the dental surgeon of today is doing his best in his overcrowded day, the Government, apparently with your approval, is going back half a century

Does the medical profession not realise that this dilution of the dental profession is not in the interest of either the profession or the public, it is Government chicanery to attain cheap dentistry, and the shortage of dentists is being put to good use

The medical profession is being abused because of possible overcrowding Were there a shortage of doctors, I wonder what type of ancillary would be introduced

Instead of quarrelling about the fact that young dentists by hard work and long hours can earn professional remuneration, while young doctors are being exploited, as complementary professions each should be understanding of and sympathetic to the other and work together for their mutual benefit

If the ancillary experiment is a success and I have no doubt that it will be, we shall see the beginning of the end of dentistry as a profession and a distinct fall in the standard of dental treatment If the new ancillary training hospital at New Cross was to be used for the training of dental surgeons, and if the project Mr Walker-Smith has in hand of admitting 900 dental students per annum was speeded up, there would soon be no shortage of dentists

London, N W 7

M CHALMERS

CLASSIFICATION OF CHRONIC BRONCHITIS

SIR,—Your annotation of Dec 19 rightly draws attention to the necessity for an agreed nomenclature in regard to the clinical condition which, in this country, is traditionally called "chronic bronchitis" At present we are largely ignorant of the natural history and causes of this disease, so that any classification to be generally acceptable must be simple and based on easily distinguishable clinical features Fletcher's excellent classification,[1] to which you refer, points the way, but is too elaborate for widespread use If kept to its three broad categories, it is a useful basis from which further subdivisions may be made

The first type which Fletcher has called "simple chronic bronchitis" would surely be better termed "bronchorrhœa" This avoids the suggestion inherent in the word "bronchitis" that the process is inflammatory, and so far as I can ascertain from medical dictionaries, simply means "an excessive discharge of mucus from the air passages of the lungs", and has no other connotation

Fletcher postulates infection as the dominant feature of his second type It may be only pedantic to argue that mucopurulent sputum, or recurrent chest illness, is not always evidence of infection, but certainly there is a difference between the hearsay evidence of the patient reporting thick yellow phlegm, and the physician actually observing purulent sputum, just as there is a difference in the readiness of different patients to admit to "recurrent chest illness" Nevertheless, it is this second stage of bronchitic disease which is likely to be the most important clinically during the next few years, and an acceptable classification could usefully postulate the objective observation of the patient's purulent sputum

Until recently, any definition of ventilatory impairment has been difficult because subjective appraisal differs widely Fortunately, Wright's peak expiratory flow-meter now affords a means of evaluation of ventilatory capacity which can be measured easily and quickly in any hospital outpatient department, and a peak expiratory flow-rate of, say, less than 300 litres per minute could be arbitrarily accepted as a definition of moderate ventilatory impairment in a bronchitic subject

The three stages of bronchitic disease might therefore be (1) bronchorrhœa, (2) recurrent infective bronchitis, (3) recurrent bronchitis with ventilatory impairment All these can, of course, be subdivided

If some responsible body closely associated with research in this field arbitrarily ventured to postulate its definitions, it might be a considerable encouragement to individual research-workers to publish their findings in terms of such definitions which would facilitate the comparison of published work

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W H TATTERSALL

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[1] *Amer Rev resp Dis* 1959, 85, 493

PYELOGRAPHY IN URINARY INFECTION

SIR,—" Pyelography not yet justified " This statement in Dr James' article (Dec 5) prompts me to ask again when is pyelography justified in renal-tract infections? While R M O at Salisbury General Infirmary recently, I included intravenous pyelography as a routine investigation in all acute renal-tract infections amongst the nursing staff The total number of such cases was quite low but, to my surprise, three pyelograms revealed evidence suggestive of obstruction in two there was persistent unilateral ureteric kinking and in a third a double ureter was shown on one side As these were all first infections in otherwise healthy young girls surgical intervention was not sought I am still wondering whether this was the correct attitude or not

There is a wealth [1] [2] of experimental and presumptive clinical evidence showing a correlation between obstruction and renal-tract infection Of the possible permanent sequelæ to such infection we are only too well aware That obstruction was a possible factor in the pathophysiology of these cases I had little doubt Yet I am sure most surgeons would be loathe to intervene in the absence of more positive evidence, such as persistent or recurring infections, or calyceal distortion Logic teaches that this is obviously too late and that many cases of occult persistent infection will be missed Nevertheless until we are prepared to investigate and treat actively all cases of " minor " anatomical disturbance I see little point in routine pyelography I wonder does Dr James think likewise?

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JAMES G DEVLIN

TROPHOBLAST AND ITS TUMOURS

SIR,—If the trophoblast is a homograft, the full implications do not appear to be yet realised Surely if tolerance to a homograft can be induced in a fœtus or newborn animal, but not an adult animal, by injection of donor cells it is an unjustified extrapolation to suggest that a similar mechanism occurs in the human adult pregnant female host This topic is not new, in your columns I pointed out ten years ago [3] in detail the inconsistencies that the present hypothesis leads to and suggested an alternative The alternative is that the trophoblast is an autograft, at least the syncytial portion of it, and derived from the granulosa cells that cover the ovum when it leaves the follicle

Unorthodox as this suggestion is it at least makes sense, which the present orthodoxy does not I suggest that the main function of the syncytium is to protect the fœtus from the homograft reaction of the mother, and perhaps vice versa to protect the mother from the fœtus Remember that however separate the fœtus may be from the mother the syncytium is as intimately involved in the maternal circulation as any cells can be

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ISRAEL GORDON
Medical Officer of Health

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[1] *Lancet*, 1959, i, 614
[2] *ibid* p 1265
[3] Gordon, I *Lancet*, 1949, i, 807

MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

SIR,—The article by Dr Coffey and Professor Jessop (Nov 28) merits further comment, especially in view of two contradictory reports on this subject In all likelihood, these reports were not available to Dr Coffey and Professor Jessop when they completed their study

Wilson and his co-workers as a result of their investigation [1] concluded that " No significant teratogenic effect of Asian influenza was demonstrated " It is to be noted that the presence or absence of influenza in the patients they studied was confirmed by hæmagglutination—inhibition titre determinations

Walker and McKee [2] have concluded that " there was no apparent alteration in the number of anomalies in the infants of mothers who had Asian influenza during their pregnancy" In this study serological tests for influenza similar to those employed in Wilson's investigation were also carried out

On the basis of the findings of Walker and Wilson one might well question the implications of the Dublin study Moreover, the methodology of selecting patients for inclusion in the study on the basis of self-diagnosis is vulnerable to criticism This is so, not so much (in this instance of a disease with a high attack-rate) because those replying in the affirmative may not have had the disease, but, as Walker's study points out, because those replying in the negative may very well have had the disease

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GEORGE X TRIMBLE
Director of Medical Education

FORMATION OF RENAL CALCULI

SIR,—I was very interested indeed to read your annotation of Oct 24

I have been carrying out a small experiment to try to confirm or refute the claim that the administration of salicylates prevents the formation of urinary calculi

Medo-Chemicals Ltd have very kindly supplied me with a stock of their ' Salimed ' tablets and also some pseudo-salimed tablets, and I have been administering these to an unselected group of patients who have had recurrent urinary calculi, but in whom there is no local predisposing cause to recurrence, such as chronic infection or stasis This is obviously a very long-term type of investigation and as yet it is not possible to draw any conclusions

I know that claims have been made in America, both for and against its administration, but I feel that both these investigations were not sufficiently selective or continued for a sufficient length of time to justify the conclusions I hope in a few years' time that I shall be able to give some results which may help to decide whether there is any value in the administration of salicylates, or salicylate-containing substances, to patients with recurrent calculi.

Hove, Sussex

S H C. CLARKE

ÆTIOLOGY OF LEUKÆMIA

SIR,—The theories discussed in your leading article [3] on the ætiology of leukæmia are intriguing However, some results of our studies on human leukæmic leukocytes in vitro are in disagreement, not only with the concept of chronic leukæmia as a conditioned neoplasm resulting from deficiency of a blood-borne growth inhibitor but also with the thesis that autonomy of leukæmic cells (i e, in acute leukæmia) might be specifically indicated by an abnormal chromosomal pattern We failed to find any chromosomal abnormality in the three cases of *acute* granulocytic leukæmia reported some time ago,[4] and more recently we have found a small, but definite, abnormality, a minute replacing one of the 46 normal chromosomes, in the 2 cases of *chronic* granulocytic leukæmia investigated [5]

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[1] Wilson M G, Heins, H L, Imagawa, D T, Adams J M. *J Amer med Ass* 1959, 171, 638
[2] Walker, W M., McKee, A. P *Obstet Gynec* 1959, 13, 394
[3] *Lancet* 1959, ii, 447
[4] Nowell, P Hungerford D, Brooks, C *Proc Amer Ass Cancer Res* 1958 2, 331
[5] Nowell, P, Hungerford, D (to be published)

Further, in studies involving both acute and chronic granulocytic leukæmia and acute monocytic leukæmia, we have been thus far, unable to show any difference in either mitotic activity or differentiation of leukæmic cells in vitro, whether grown in normal or in leukæmic plasma[6]

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P C NOWELL

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D A HUNGERFORD

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—The problem of inadequate sources of blood for replacement after massive hæmorrhage is probably the main bugbear of surgery in many hospitals overseas Fortunately, as Mr Azie points out (Dec 12), in the patient with ectopic gestation we have adequate blood reserves available—her own

In this hospital the patient is sent immediately to theatre, and a drip started Anæsthesia takes no longer than adequate scrubbing by the surgeon, and saves the patient from the added shock of seeing her own blood being, as she thinks, sacrificed

Through a small nick in the peritoneum a fine "sieve"-ended cannula is inserted into the cavity and the free blood drawn into sterile citrated bottles while adequate exposure is made in the more superficial layers This decompresses the abdomen and minimises blood wastage The blood collected is returned to the patient through the drip at maximum speed, the first litre being given in 5 minutes The subsequent rate is controlled by the patient's condition The blood-bottle filters seldom show clot, and we have now records of over fifty cases without mishap, and up to 2 litres of peritoneal blood have been given

Theoretically, this technique is open to objections, but to those of us who serve on the frontiers of medicine the consistently good result justifies its use We have tried the collecting, whipping, straining, and reinjecting methods and have rejected them in favour of a technique as safe as it is simple The patient is back in bed within half an hour often apparently little the worse for her experience, except for the loss of her tube

Finally, Sir, may I express my appreciation of the fact that your highly scientific journal finds space for the description of techniques which, though unnecessary in highly developed countries, may still save many lives in less fortunate areas

Kwahu Hospital
Mpraeso,
Ghana

J ASHFORD HYDE

SIR —I was interested in the recent letters from Mr Azie (Dec 12) and Prof Chassar Moir (Jan 2) on emergency resuscitation by the use of the patient's own blood removed from the abdomen and think it may be of interest to record an early instance of the use of this method

In the spring of 1915 at Bethune I saw Capt John Fraser (later Prof Sir John Fraser) use blood removed from the abdomen of a man suffering from a gunshot wound, for transfusion after filtration through silk I do not know whether this was ever recorded elsewhere but at that time, when blood for transfusion was unobtainable, the method was regarded as unique

Ickleton Saffron Walden

CLAUDE FRANKAU

URINARY INFECTION IN THE NEWBORN

SIR,—I am grateful to Dr Brown (Dec 19) and Dr McNicholl (Jan 2) for their comments on my paper of Dec 5 I regret that the pus-cell counts were omitted and they are given in the accompanying table

—		Growth of organisms			
		Sterile	Scanty	Moderate	Heavy
No of cases		4	82	9	5
Pus-cell count	Males		141→10 750→20 Others less than 21	10 138→10	27 1000→48,000 1000→1150
	Females	Less than 33	Less than 40	108→21 261→52 Others less than 32	1000→1200 11

I agree with Dr Brown that the criteria for diagnosis must be carefully assessed, and for this reason I stressed that the cell-counts in the urine must be repeated in cases of doubt, especially where there is lack of correlation between cell-count and culture He will also see that a second count is recorded in the chart reproduced in my paper

I have observed that the incidence of neonatal urinary infection varies from time to time in the same maternity unit even when constant criteria are used for diagnosis, but for this I can give no explanation

Pus-cell counts in a measured quantity of uncentrifuged urine can be reported with accuracy and results are comparable from any hospital or laboratory, whereas microscopic-field counts must vary according to the size of the drop held by the coverslip

Stansfeld[1] reported that an average of 1 pus cell per high power field was approximately equivalent to 250-500 pus cells per c mm of uncentrifuged urine It is therefore evident that this method of urine examination is unsuitable for demonstrating urinary infection in newborn babies

I am most interested in Dr McNicholl's report of hæmolytic anæmia associated with renal infection I have had 2 similar cases, but in each of them the blood-culture for *Escherichia coli* was positive I have observed no other cases

London W 1

URSULA JAMES

PRISONS

SIR —Your leader of Dec 5 rightly applauds the work of the prison service in the face of an increasing prison population, but makes no mention of the appalling physical conditions existing in some prisons today Improvements in the prisoners' uniform and relaxation of the "silence" rule in workshops can only partially alleviate the problems posed by buildings which are frequently over a hundred years old, inadequately heated, and provided with sanitation barely fit for animals

An offender is sent to prison *as a punishment* and not *for punishment*[2] As you have stated, many youths wait for two months in local prisons before reaching reception centres It might usefully be pointed out that, because of the rapidly changing population, the cell blocks in which they are housed (e g, at Wormwood Scrubs) are actually in a worse state than those housing the more permanent adult prisoners The stench of urine in these blocks is overpowering It is a sorry thing that those in authority are apparently as impervious to these facts as the prison walls to the heat of a summer's day

Yale University School of Medicine
New Haven, Connecticut

DENIS ABELSON

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[6] Nowell P *Exp cell Res* (in the press)

[1] *Proc R Soc Med* 1951, 47, 632

[2] Prisons and Borstals H M Stationery Office, 1957

HIRSUTISM AFTER ADRENALECTOMY

SIR,—I was very interested in the report by Professor Bruce and his colleagues (Dec 12), who noted vigorous acial hair growth after bilateral adrenalectomy and gonadectomy

Thomas and I, in a study of some 600 patients,[1] found an ncrease in facial hair growth and disappearance of hair from he lower abdomen with advancing years Gallwey and I, in a further unpublished study of about 400 patients, confirmed this and found a similar disappearance of hair at eight other sites Clearly facial hair behaves differently from hair elsewhere after the menopause, some factor peculiar to this area must be presumed The observations of Strong, Bruce, and Falconer suggest that this is non-hormonal, though a release from hormonal influence may be involved.

North Middlesex Hospital,
London, N 18

DAVID FERRIMAN

TREATMENT OF INOPERABLE CANCER WITH 5-FLUOROURACIL AND IRRADIATION

SIR,—Curren et al [2,3] have shown that the administration of 5-fluorouracil, a pyrimidine antagonist, produces significant objective improvement in an impressive number of patients with far-advanced metastatic neoplastic disease The most favourable results were in carcinoma of the breast, ovary, large bowel, and rectum and in hepatoma Variable responses were noted in a number of neoplasms, including carcinoma of the cervix No response was obtained in carcinoma of the lung, stomach pancreas, and kidney, and in a variety of other tumours, including embryonal-cell carcinoma of the testis Tumour regression was observed only in patients treated to a toxic level Toxicity was characterised by stomatitis and diarrhœa, and later by suppression of hæmatopoiesis, and severe toxicity by ulcerative lesions in the alimentary canal

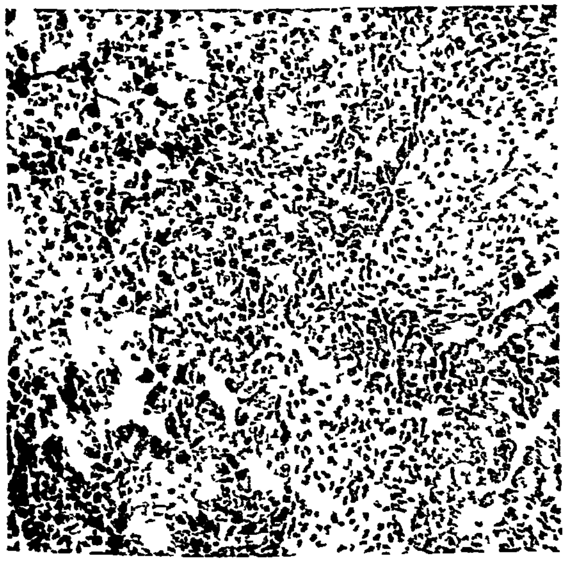

Fig 1—Embryonal-cell carcinoma.

In the hope of avoiding moderate to severe toxicity, we decided to administer 5-fluorouracil in sub-toxic doses concomitantly with deep-ray therapy

Initially, patients with inoperable carcinomas of the head and neck and of the lung were selected for combination therapy Subsequently, other types of malignant disease have been treated by this means also Treatment consisted of the intravenous administration of 5-fluorouracil throughout the period of irradiation, except in isolated instances when 5-fluorouracil therapy was discontinued temporarily because of manifestations of toxicity (stomatitis, diarrhœa, or leucopenia) The dosage was as follows 15 mg per kg per day for 4 days, 7 5 mg per kg on the fifth day, and thereafter 7 5 mg per kg twice weekly until the course of irradiation had been completed.

In 3 patients with undifferentiated squamous-cell carcinoma of the lung, in 2 patients with pulmonary metastases secondary to embryonal-cell carcinoma of the testis and to adenocarcinoma of the rectum, and in 1 patient with lymphoepithelioma, 5-fluorouracil and X-ray therapy were stopped when a radiation (tumour) dose of 2000–2250r had been given Chest films were taken before and two weeks after completion of therapy All other patients in our series received larger doses of radiation than those mentioned above

All the patients who received 2000r plus 5-fluorouracil showed rapid and significant regression of their lesions except for the patient with pulmonary metastases secondary to adenocarcinoma of the rectum These observations suggest that either there may be an additive effect when the two treatments are used simultaneously or that one method may potentiate the anti-tumour effect of the other Since 5-fluorouracil alone in carcinoma of the lung did not produce tumour regression in the cases of Curren et al, and since a tumour dose of 2000r administered alone rarely produces a significant response in this type of tumour, it is possible that 5-fluorouracil actually increases tumour radiosensitivity

To date, excellent initial responses to combined therapy have been observed in 6 of 8 squamous-cell carcinomas of the lung, in 4 of 5 squamous-cell carcinomas of the head and neck, and in 1 patient each with embryonal-cell carcinoma of the testis, adenocarcinoma of the breast, undifferentiated carcinoma (primary site unknown), and reticulum-cell sarcoma

A man aged 23 years had a right orchidectomy and bilateral iliac and preaortic lymph-node dissections in March, 1958, for embryonal-cell carcinoma (fig 1) This was followed by X-ray treatment to the retroperitoneal area during the spring of 1958 The patient was well until March, 1959, when chest pain, hæmoptysis, and exertional dyspnœa developed. A chest film revealed large bilateral pulmonary metastases (fig 2a) An Ascheim-Zondek test was negative at 500 μ per litre. Urinary 17-ketosteroids were 9 0 mg per 24 hours and 11-hydroxysteroids 5 0 mg per 24 hours Combined treatment was begun on April 13 and completed on April 28 (2000r, esti-

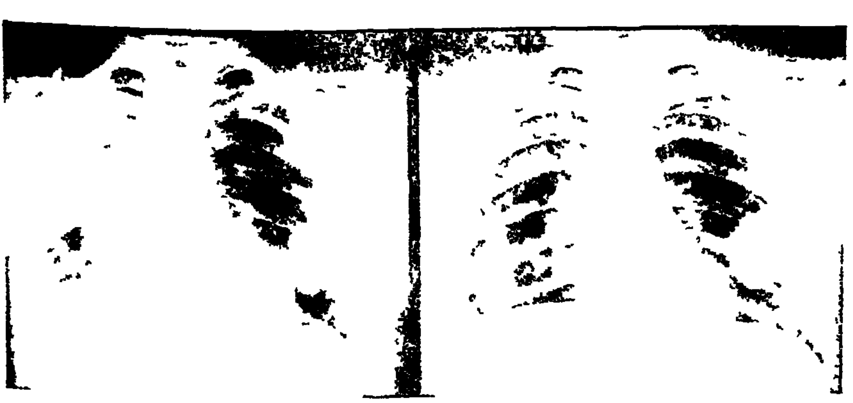

Fig 2—(a) Chest radiograph before combined treatment (March 20) (b) after treatment (May 12) with 5-fluorouracil and irradiation of right hilar mass.

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1 Thomas, P K., Ferriman, D G *Amer J phys Anthrop* 1957, 15, 171
2 Curren, A R, Ansfield, F J, McIver, F A, Waisman, H A, Heidelberger, C *Cancer Res* 1958, 18, 478
3 Ansfield, F J, Curren, A R *J nat Cancer Inst* 1959, 22, 497

mated tumour dose to the right hilar mass, plus 6170 mg of 5-fluorouracil) The irradiated metastatic lesion in the right hilum regressed (fig 2b), but the non-irradiated lesion in the left lung did not

Obviously, long-term studies with large numbers of cases will be necessary before a definitive evaluation of combined therapy versus irradiation alone can be attempted

We wish to thank Hoffmann-LaRoche, Inc, Nutley, N J, and the Cancer Chemotherapy National Service Centre for generously supplying 5-fluorouracil for this study This study was supported in part by grants-in-aid from the National Cancer Institute, United States Department of Health, Education and Welfare

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ALCOHOLISM AND HEPATIC CIRRHOSIS

SIR,—Your report (Dec 12) of the meeting on alcoholism and cirrhosis of the liver, held in New York, mentions estimates that " one in sixteen of those who take alcohol becomes an alcoholic and about 8% of these will develop cirrhosis " Figures of 8% or 9% are usually quoted, however, as the proportion among " chronic alcoholics " who develop cirrhosis,[1] [2] and by no means all alcoholics show the bodily and mental disorders which according to the definition of Haggard and Jellinek [1] and the W H O alcoholism subcommittee [3] denote " chronic alcoholism " For example, the proportion of " chronic alcoholics " among all alcoholics in the United States, according to Jellinek's latest estimates, is less than 20% [2] According to the W H O subcommittee, the term " alcoholics " includes not only those excessive drinkers who show " an interference with their bodily and mental health " but also those in whom drinking interferes with " their interpersonal relations and their smooth social and economic functioning ", and those " who show the prodromal signs of such developments " [4] Thus much less than 8% of all alcoholics can be expected to develop liver cirrhosis

As the figures of 8% or 9% refer to the incidence of alcoholic cirrhosis of the liver (among alcoholics with complications) relative to other complications of alcoholism, a decrease of other complications would automatically increase the relative incidence of liver cirrhosis among chronic alcoholics In North America, because of a considerable fall between 1943 and 1950, in the incidence of alcoholic polyneuropathy and of certain other complications, the relative incidence of liver cirrhosis among alcoholics with complications is now estimated by Jellinek as amounting to 14% or 16% Jellinek states, however, that these changes in the relative incidence of alcoholic complications have not occurred in Europe [2]

Much more common, of course, in alcoholics than liver cirrhosis is fatty infiltration of the liver [1] It seems that in this country the great majority of alcoholics entering mental hospitals which take a special interest in alcoholism hardly ever show clinical evidence of liver damage Such people often show abnormalities when investigated with a battery of liver-function tests [5] After a period of abstinence and a balanced vitamin-supplemented diet such laboratory abnormalities often prove reversible, thus *corresponding to the improvement* noted in your report.

Liver cirrhosis is a very important complication of alcoholism, but it must not be forgotten that it occurs in a relatively small minority of alcoholics only, and in these a a relatively late stage of their alcoholic career In view of the deterioration of judgment and performance with even small quantities of alcohol,[6] it is not surprising that a great many alcoholics show evidence of behaviour disturbance long before they enter their " chronic phase " and possibly develop liver cirrhosis [7] The W H O expert committee on alcohol and alcoholism has pointed out that " while the physical and mental sequelæ of alcoholism have always been recognised as medical disorders, there has been much less readiness to regard as matter of medical concern the behaviour which results in these complications " [8] At present many alcoholics are not recognised as such till they have arrived at their late " chronic " stages *Medical education on alcoholism, therefore, should not be* exclusively or even predominantly concerned with the teaching of late complications but should lay due emphasis on the much more common and earlier disorders of conduct The teaching of medical students will then further contribute to the aim so rightly stressed in your report that " every effort should be made both to secure early diagnosis and to ensure continued abstinence "

St Bernard's Hospital,
Southall, Middlesex

M M Glatt

THE COST OF DRUG TREATMENT

SIR,—It is to be hoped that the departments of the Ministry of Health concerned with prescribing and its cost to the N H S will ponder well the revealing article by Dr Miller and Dr Smith (Jan 2) They rightly draw attention to the paradoxical economics of general-practitioner prescribing with especial relation to long-term saving of inpatient costs and national productivity by the use of some of the more expensive drugs in general practice

Over the head of every N H S practitioner hangs the spectre of a prescribing investigation with the possible (but very uncommon) consequence of deduction from his quarterly cheque of the cost of certain drugs considered necessary by him for his patients but not, apparently, by the powers that be These inquiries follow periods of full pricing of all prescriptions by the executive councils at intervals in each year In any case, local pharmacists will know in advance when " pricing " will be in operation and can warn doctors beforehand

As I have pointed out previously,[9] little or no attempt is made by drug manufacturers to inform doctors of the total cost to the N H S of their products The basic cost represents an artificial and in some cases minute proportion of the total cost of a prescription, as Dr Miller and Dr Smith have noted, and has a much more attractive appearance on advertising literature

Most of us suffer from the rapacity of patients, and all of us realise that refusal to prescribe a substance demanded by a patient against our better judgment may possibly lead to his transfer to another doctor who will prescribe it regularly with a clear conscience, with resulting loss of capitation fees to ourselves I wonder how many practices have been built up by high prescribing relative to neighbouring doctors at the expense of the national drug bill Complaisant negligence by doctors is perhaps a subconscious defence mechanism to safeguard our incomes! To achieve a balance in this respect is one of the most disturbing aspects of practice to some of us who work in areas where standards of living are increasing

London N W 2

D S Nachshen

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[1] Haggard, H W, Jellinek, E M Alcohol Explored, pp 177, 182, 189 New York, 1950
[2] Jellinek, E M *Quart J Stud Alc* 1959, 20, 261
[3] *World Hlth Org techn Rep Ser* 1951, 42, 19
[4] *ibid* 1952, 48, 16
[5] Kay, W W, Murfitt, K C, Glatt, M M *J ment Sc* 1959, 105, 748

[6] See *Lancet*, 1960, i, 41
[7] *World Hlth Org techn Rep Ser* 1952, 48, 29
[8] *ibid* 1955, 94, 3
[9] *Brit med J* 1959, ii, suppl p 20

Obituary

WILLIAM ERRINGTON HUME

Kt., C.M.G., M.A., M D Cantab, F.R.C.P

Sir William Hume's early election to the staff of the Royal Victoria Infirmary gave him an unusually effective working span, but its length was appropriate to the work which he accomplished. The Newcastle medical school valued his contribution as a pioneer of scientific medicine, an outstanding teacher, and an upright man. He died on Jan 1 at the age of 80

His father, George Haliburton Hume, practised as a surgeon in Newcastle upon Tyne and took a large part in the building of the Royal Victoria Infirmary Hume himself was educated at Repton School and Pembroke College, Cambridge At the London Hospital he was clerk to Sir Bertrand Dawson, and after qualifying in 1904 he returned to Newcastle to hold a succession of resident appointments He was senior house-physician at the Royal Victoria Infirmary when it moved into its new buildings in 1906 Two years later he was elected to the staff and was also appointed demonstrator in pathology at Durham University From the first he was a brilliant teacher and his ward rounds and museum classes were always packed

When the war began in 1914 Hume, by virtue of his hospital appointment, became a lieut.-colonel in the 1st Northern General Hospital, but he was anxious to serve abroad and joined a casualty-clearing station though this meant a loss of rank. Soon afterward he was posted to Boulogne, where he joined his old chief Dawson in the organisation of centres for cases of D.A.H They also began an investigation into spirochætal jaundice, which S P. Bedson was invited to join He writes

"Hume and Dawson were interested in the cases of Weil's disease which were occurring in our troops in the wet trenches of Flanders, and Hume, knowing that I had been unable to obtain suitable war work, suggested to Dawson that it might be possible to have me transferred to them and made responsible for the laboratory side of their investigations This was arranged and I joined them to spend three most pleasant and valuable years working with them. Hume and I were billeted together in Wimereux near to the house in which I had installed my laboratory and next door to Lord Dawson and to a refugee French family from Lille. Friendship with our French neighbours prospered and much of our leisure was spent enjoying the delightful hospitality of Madame Tissevre and her family, Hume later married the elder daughter Not only did I find Hume a most valuable colleague, but he proved also to be a delightful companion. He was entirely unselfish, had a real sense of humour, was not inappreciative of the good things of life and was withal of a complete integrity The time spent in his company was the basis of a friendship which I shall always cherish."

Before the end of the war Hume was appointed consulting physician to the 1st Army, and for this work and his research on poison gas he was mentioned in despatches and received the C.M G After his return to civilian practice his papers on war nephritis and encephalitis lethargica were useful continuations of his work during these war years But his chief interest lay of course in cardiology Early in his days at Newcastle he studied intensively the heart rhythm in diphtheria As early as 1913 he had described what is now called auricular flutter, and as the subject of his Bradshaw lectures in 1917 to the Royal College of Physicians of London he chose paroxysmal tachycardia

He was elected F.R.C.P that year, and later he served the college as censor and as senior censor in 1941 In 1943 he gave a war-time Harveian oration with the appropriate title of "the physician in war in Harvey's time and after" In 1943 he had been appointed to the chair of medicine at Newcastle, but in 1940 on his retirement from his hospital appointment he resigned.

For some years he remained on the staff of the Newcastle General Hospital and he was largely responsible for setting up the regional cardiovascular centre. He gave much other counsel to the organisation of the services of the region in the early days of the National Health Service. He was knighted in 1952, the year when increasing ill health finally forced him to retire from practice

H G M recalls the advice he received when he became Dr Hume's house-physician in 1938 "Have every patient electrocardiographed, and always carry twenty 'Gold Flake' in your pocket"

"Hume (he continues) was a superb clinician, and the contrast between his astute empiricism and the more speculative approach of his assistant physician, James Spence, was a rewarding and sometimes diverting experience

"Hume held the chair of medicine largely by virtue of his clinical seniority Such a procedure would be unthinkable today, but in retrospect it furnished here and elsewhere a cadre of clinical professors many of whom yield nothing in eminence or achievement to their successors appointed on other grounds Of such was William Hume, a man of extraordinary mental acuteness, with no time whatever for cant or pretence, able to diagnose a humbug with the same instantaneous flair as he did auricular flutter His systematic lectures were unforgettable. As he entered the theatre he peppered members of the audience with searching questions based on the subject-matter of the previous meeting These lectures represented the essence of a vast personal experience, sifted by unflagging and meticulous observation. He never used a note or quoted an authority, but he always had an appropriate clinical anecdote at his fingertips, drawn from his war-time service in France, his experience as an outstanding witness in the courts, or his daily work as a busy and successful consultant physician in the colliery villages and great houses of Northumberland and Durham.

"One of a generation of great general physicians, many of whom were his close friends, Hume nevertheless encouraged genuine specialisation, particularly in his own interest of cardiology He maintained however an amused contempt for some of the more recent synthetic specialties, and for what he regarded as the essential triviality of much that currently passes for research.

"He lived and breathed medicine. His great delight was fishing, but even when he went up for a few days on the Border, a couple of beds were always kept empty for the cases, whether of heart-block, cerebral tumour, or obscure pyrexia, that were sure to be 'rung in' from Wooler or further north. He retained this vivid interest in medicine until the end. Only a few weeks ago he summoned me to his home by a peremptory telephone-call to discuss and criticise a paper in preparation, about which he had heard in the course of the medical gossip with which he always loved to surround himself

"Truth to tell—and although he was never anything but kind—I think we were all just a little frightened of him. His juniors' only consolation was that Knowledge and Wisdom so palpably superior, though so lightly worn, seemed to be not without a slightly intimidating effect on many of his near-contemporaries"

Lord Moran writes

"I think of William Hume with Dawson and Wilmot Herringham as central figures of another time. Consulting physician to the British Forces in France in the First War, he was Dawson's right-hand man at Boulogne, and Herringham, who was inclined to be impatient with mediocrity, thought well of him After the war, Hume was one of the three founders of the Cardiac Club, where he was well liked as a keen, cheerful, and kindly man And John Parkinson has said that when they met he felt invigorated It is now a quarter of a century since he was a councillor at the College, having already given the Bradshaw lecture, soon he became a censor and a little later gave the Harveian oration I read what he wrote, for it was salted by horse-sense and always to the point Besides, he had the literary art

"About William Hume there was an air of distinction Moreover he was a master of his craft I think of him as among the two or three physicians in the Provinces whom I most wished visitors to England to meet He was a brave soul, though he had to contend with years of pain and crippling illness, it never seemed to get him down Lately he was so much in pain, so frail, and so weak that I used to telephone when I was in Newcastle to find whether he felt equal to a visitor But he was always ready to talk on anything save his own illness, and he never lost his healthy outlook I can only guess what he owed to the wisdom and understanding of his wife.

"William Hume was a considerable figure in the North of England and I count him in the direct line of descent from those English physicians who, proficient in their art, were also men of affairs, the kind of men who had influence beyond their own calling"

Sir William Hume is survived by his wife, three daughters, and two sons One of his sons is in practice in Sunderland, and his eldest daughter is married to Sir John Charles

JOHN ERNEST ALFRED UNDERWOOD

C B E , M B , B Sc Lond , D P H

Dr J E A Underwood, a former principal medical officer of the Ministry of Education, died suddenly on Dec 31, at the age of 73

The son of Ernest Underwood, of Blackheath, he was educated at Blackheath School, University College, London, where he was president of the Union, and University College Hospital He graduated B SC in 1910 and qualified in 1915, when he joined the R A.M C , serving in France and India On his return to civilian life he took the M.B and the D P H , and in 1921 he became medical officer of health and school medical officer for Willesden He joined the staff of the Board of Education in 1925 and succeeded Dr J A Glover as principal medical officer in 1941 He was appointed C B E in 1948 and retired in 1951

Underwood was particularly interested in the problems of children who were blind or deaf, and he represented the Government at the international conference on the welfare of the blind held in New York, in 1931 He was secretary of the Committee on Partially Sighted Children that reported in 1934, and was vice-chairman of the one set up in the same year to inquire into problems relating to children with defective hearing In his later years at the Ministry of Education he became increasingly concerned with emotionally disturbed children, and when the Committee on Maladjusted Children was appointed in 1950 he was made chairman The work of this committee occupied much of his time during the first years of his retirement The committee's main recommendations were accepted by the Government and were the subject of recent circulars from the Ministries of Education and Health on the development of child-guidance services From early in his retirement he was a member of the governing bodies of Moor House School for Children with Speech Defect, Oxted, and the Heritage Craft Schools and Hospitals, Chailey, and also of the Mid-Sussex hospital management committee

A colleague writes

"Underwood read widely and he had a good collection of books His presidential address to the Medical Officers of Schools Association was a scholarly review of the allusions to medicine in the works of Shakespeare He enjoyed foreign travel He was somewhat reserved in manner but to those who knew him well he was an excellent companion, with a nice, but never malicious, wit and a great depth of common sense He was never known to lose his temper and was tolerant to a degree that sometimes became embarrassing

"On the day of his death, as was his custom, he went for an afternoon walk with his collie dog across the fields near his home in Sussex When darkness came down and he did not return a search party went out, but his body was not found until next morning he lay in the field where he collapsed, guarded by his dog who, at first, fiercely resisted the searchers"

Dr Underwood is survived by his widow, Catherine German, whom he married in 1923

JOHN RITCHIE

M B Edin , F R C P E , D P H

Dr John Ritchie, formerly medical officer of health for Dumfriesshire, died in Edinburgh on Dec 24

Born and educated at Brechin, Angus, he qualified from Edinburgh University in 1906 and took the D P H the following year After holding appointments in the City Hospital, Edinburgh, as resident, senior assistant, and bacteriologist, he was appointed depute medical officer of health and bacteriologist to the County of Dumfries where he spent the rest of his career He became M O H in 1924 and he retired in 1947

In 1935 he was appointed to the General Medical Council as Crown nominee for Scotland and he held this appointment for ten years, serving also as chairman of the Council's public-health committee from 1939 to 1945 He was a member of the National Insurance Advisory Committee from 1947 to 1952

He retired to Edinburgh in 1947 and was soon taking an active part in the medical affairs of the city, especially in the Royal College of Physicians. He became superintendent of the College laboratory in 1948 and was the last of a long line of distinguished superintendents, for the activities of the laboratory ceased in 1950 Later he was honorary librarian of the College, a position from which he only recently resigned He had a deep interest in medical history and made many contributions to the subject, including a history of the laboratory of the College He was a founder member of the Scottish Society of the History of Medicine, serving as its president from 1951 to 1954

A colleague writes

"No more will we see the familiar erect figure of Dr Ritchie in the precincts of the College of Physicians or of the many libraries which were the great centres of his interest after he retired to Edinburgh He was a prodigious worker resembling in many respects Osler of whom he was a keen admirer A copious note-taker, all items which interested him were entered into his commonplace books and all carefully indexed Thus it was that his contributions to medical and medico-historical literature were fully documented and appropriately illustrated by well-chosen examples In his earlier years he had thought of becoming a naval architect, and he had a keen appreciation of art His letters and reports were often enlivened by the artistic touch, and by the fitting phrase for he was a man of wide reading and culture He had, too, a great gift for short-story writing, mainly in lighter vein, and contributed to various magazines For all his accomplishments and ability, he was a quiet self-effacing man who loved the intimacy of the family circle and deliberately shunned the public eye"

CEDRIC SYDNEY LANE-ROBERTS

C V O, M S Lond, F.R C S, F R.C O G

Mr Cedric Lane-Roberts, consulting obstetrical surgeon to Queen Charlotte's Hospital and consulting gynæcological surgeon to the Royal Northern Hospital, London, died on Dec 25 at the age of 71

He was the third son of the late Lieut -Colonel A S Roberts and he was educated at Cheltenham College and Guy's Hospital where he was distinguished as a medallist and as a rugby player He qualified in 1913 and was mentioned in despatches for his service in the R A M C during the 1914–18 war After demobilisation he held for a time the appointment of tutor in obstetrics and resident medical officer at Leeds Maternity Hospital In 1920 he took the M S and the F R C S, and soon afterwards he returned to London on his appointment as chief assistant in the women's department and obstetric tutor at St Bartholomew's Hospital Later he was appointed to the staffs of Queen Charlotte's Hospital and the Royal Northern Hospital and he also built up a large consultant practice. He contributed to the *Royal Northern Operative Surgery* and the *Queen Charlotte's Practice of Obstetrics* He was joint author of *Sterility and Impaired Fertility*

He was a foundation member of the Royal College of Obstetricians and Gynæcologists and he was elected to the fellowship in 1933 He was appointed C V O in 1942

K W writes

"*Who's Who* tells you the facts about Lane-Roberts, his hospital appointments and that he played in the English Rugby Football team four times and in the Guy's Hospital team for six years, but the real Cedric Lane-Roberts, the big-hearted colleague with whom it was impossible to quarrel, is not revealed. He was undoubtedly a big, heavyweight bustling international forward, but he was big in many other fields than rugby football Never have I worked with a colleague so loyal and dependable as he, and I saw a great deal of him at the Royal Northern Hospital We were both interested in the subject of human fertility and having secured some funds from what is now the Beecham Trust we were able to establish there one of London's earliest parenthood clinics But again I am giving a lopsided account of a man who had many interests outside his professional work. One was always unearthing unexpected hobbies in him Greek architecture, ancient Chinese bronzes and lacquer work, Tibetan pictures of the Buddha, and, more prized than all these—his garden at the Mill House, Tewin"

Mr Lane-Roberts married Nell Miles-Sharp, daughter of the late D W Bain, and she died in 1954

Public Health

Infectious Diseases in England and Wales

Disease	Week ended December			
	5	12	19	26*
Diphtheria	5	17	7	2
Dysentery	723	803	910	683
Encephalitis				
Infective	1	1	3	5
Postinfectious		3	1	
Food poisoning	190	193	377	164
Measles, excluding rubella	1113	1128	1083	948
Meningococcal infection	26	16	20	14
Ophthalmia neonatorum	20	12	28	8
Paratyphoid fever	1	1	3	4
Pneumonia, primary or influenzal	305	324	325	233
Poliomyelitis				
Paralytic	11	5	4	1
Non paralytic	2	2		1
Puerperal pyrexia	156	189	174	125
Scarlet fever	1418	1537	1333	1001
Smallpox				
Tuberculosis				
Respiratory	432	434	400	262
Meninges and C.N.S	6	4	1	6
Other	44	48	42	25
Typhoid fever	3	2	2	1
Whooping-cough	739	672	561	371

* Not including late returns

Notes and News

A COLLEGE BILL

In the life of an institution, a family, or an individual, a flitting is an opportunity for repair, replacement, and renovation In preparation for its move from Pall Mall East to Regent's Park, the Royal College of Physicians is presenting a Private Bill to Parliament to modify and clarify some of its ancient rights

The first, though not perhaps the most important clause of the Bill, proposes that the college shall be called and known as "The Royal College of Physicians of London" This title is already familiar by usage and repute But in the original royal charter, granted in 1518 by King Henry VIII, the college is described as "The President and College or Commonalty of the Faculty of Physic in London", and it may be that this pleasant, if cumbersome, name is the only one it has actually been authorised to use Though the familiar form stands in the Medical Acts since 1958 the archaic form has been retained in most of the college's legal documents, including those drawn up when it moved to Pall Mall East from the City

The second clause of the new Bill deals with another difficulty which the college first met at the time of this earlier removal Under the original charter it was only empowered to hold its meetings in the City of London, and when it moved to Westminster powers had to be obtained to allow it to act there Under the new Bill, its territorial choice would be extended to the whole of England

A third clause removes a limitation imposed by the Act of 1814, which only allows the college to hold lands of an annual value not exceeding £1000 a year, a ceiling which changing values has unfortunately made unsuitable

TWO-YEAR MEDICAL SCHOOLS

In the past twelve years the John and Mary R Markle Foundation has taken a special interest in the support of young doctors planning careers in teaching and research at medical schools in the United States and Canada In the latest annual report Mr John M Russell, executive director, cites the Bayne-Jones report to the Department of Health, Education, and Welfare, which suggests that in the next ten years at least 1900 additional doctors will have to be trained One of the ways proposed for training them is to increase the number of "two-year" medical schools, which cover the first two years of the medical course and send their students elsewhere for clinical work.

In several of the large American cities the medical schools have clinical facilities not fully utilised and could handle more students, while "some colleges", Mr Russell says, "have excellent departments in the life sciences which could be expanded without great expense into a two-year medical course" Professors at these colleges may be reluctant for several good reasons "a medical school, next to the football team, can cause the most headaches in any university", and they fear that the additional tasks may mean more teaching and less research While agreeing that basic research must be protected at all costs, Mr Russell feels that the attitude toward teaching is another matter

> "The lack of interest in teaching undergraduates in American institutions with graduate schools is a curious phenomenon and seems to stem from the methods used to climb the academic ladder To get a promotion or a new job, to get tenure and more pay, it is important to publish, and to publish requires research There is, in fact, little incentive to teach However, at the graduate level teaching is favored Graduate students are involved with research, and the research usually is in the particular area of interest of the professor"

Hence "the reluctant professors should not be taken too seriously Teaching does have its satisfactions and there are ways in which the teacher can be recognized with pay, rank and tenure, while at the same time protecting his time for research."

The Foundation has distributed nearly 5½ million dollars since it was established in 1927 Its address is 511, Fifth Avenue, New York City, 17

Hellingly Hospital, Sussex

Last July the first patients were taken into the new 60-bed unit for the investigation and treatment of early psychiatric illness which has been built for Hellingly Hospital (near Hailsham) two miles from the main building It is called Amberstone Hospital, and patients are admitted on the recommendation of any member of the Hellingly consultant psychiatric staff. Instead of having an official opening, Dr David Rice (*the medical superintendent*) and his colleagues have held open days for the doctors of the neighbourhood, who were invited to meet the senior staff, discuss any subject in which they were interested, and see demonstrations of electroconvulsion therapy

The unit will take 35 female and 25 male patients Accommodation is in single rooms or in curtained cubicles in the 4-bed and 8-bed dormitories The staff is mixed one shift has a sister in charge (with a male staff nurse as second in charge) while the other shift has a charge male nurse with a female staff nurse as his first assistant.

University of Liverpool

On Wednesday, Jan 20, at 8 P M, at the Medical School, Ashton Street, Liverpool, Dr W H Taylor will give the first of eight weekly lectures on biochemical aspects of disease Tickets (£2 2*s*) may be had from the director of extramural studies, 9, Abercromby Square, Liverpool, 7

University of London

Dr D R Newth, lecturer at University College, has been appointed to the chair of biology as applied to medicine at Middlesex Hospital Medical School

The degree of M S has been conferred on Gerald Keen

University of Glasgow

Dr W M Gibson has been appointed to the chair of dental prosthetics

Royal Statistical Society

Frances Wood Prize (£50)—This prize is offered for an investigation, on statistical lines, of any problem which bears "directly or indirectly upon *economic* or *social conditions*" Competitors must be under 35 Further particulars may be had from the honorary secretaries of the society, 21, Bentinck Street, London, W 1 The closing date for entries is Dec 31

James Yearsley Lecture

Mr Ian Thorburn will deliver this lecture on Friday, March 4, at 5 P M, at 1, Wimpole Street, London, W 1 His subject will be tympanoplastic surgery

Anglo-French Exchange Bursaries

Short-term grants for work in France are offered again this year to British doctors and medical research workers by the Institut National d'Hygiene, Paris Details and application forms can be had from Dr G E W Wolstenholme, Ciba Foundation, 41, Portland Place, London, W 1 The closing date is Jan 31

Appeal to the Privy Council

Dr Kenneth Fox has lodged an appeal with the Judicial Committee of the Privy Council against the decision of the Disciplinary Committee of the General Medical Council to erase his name from the register

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Dr D A Buxton Hopkin, consultant anæsthetist at Charing Cross Hospital, London, has been appointed the first McDermott visiting professor of anesthesiology in the University of Texas The appointment is for one year and Dr Buxton Hopkin expects to take up the post early in April

On Wednesday, Jan 13, at 5 30 P M, at the Fountain Hospital, Tooting Grove, London, S W 17, Prof L S Penrose and Dr P E Polani will speak on chromosomal abnormalities in the mentally retarded

At the request of the Government of Pakistan the British Government under the auspices of the Colombo Plan, have asked Prof Charles Wells and Prof H P Gilding, as members of a Pakistan Commission to report on the health services organisation in Pakistan They leave in January for a tour of three months

Diary of the Week

JAN 10 TO 16

Tuesday, 12th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P.M Dr F Ray Bettley Effects of Soap on the Skin (Watson Sm lecture.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P.M *Psychiatry* Dr W Grey Walter, Dr W Ross Ashby, Prof Eysenck *Conditioning Theories and Their Therapeu Applications*

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M (London School of Hygiene and Tropical Medicine, Kepp Street, W C.1) *Prof J H Dible Pathology of Limb Ischæm*

ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M Mr Claude Taylor Malignant Disease of the Uterus

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, De Street, W 1
5 30 P.M Dr G F Swann Plain X-ray Changes in the Skull

MANCHESTER MEDICAL SOCIETY
8 P.M (Clinical Sciences Building, York Place, Manchester) *Surg* Prof A M Boyd Self-inflicted Injuries

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M. (General Infirmary at Leeds) Mr T P S Powell Cortic *Representation of Somatic Sensation*

Wednesday, 13th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
2 P.M *Dr P L Mollison Destruction of Red Cells by Immunologic Mechanisms*

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5.30 P.M Dr Arthur Tickner Serum Proteins in Skin Disease

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W.3
5 P.M. Dr E H Hudson The Changing Face of Chest Disease.

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (18, Nicolson Street, Edinburgh) Lord Kilbrandon Comm Interests

ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Stree Glasgow
5 P M Sir Gordon Gordon-Taylor *Mars and Æsculapius* (Flemin lecture)

Thursday, 14th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M Prof J W Crofton Tuberculosis Undefeated (Marc Dan lecture)

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C.2
5 P.M *Sir Walter Mercer Some Edinburgh Pioneers in Orthopæd Surgery* (Robert Jones lecture)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P M (London School of Hygiene and Tropical Medicine) Prof H L Sheehan Infarction

INSTITUTE OF DERMATOLOGY
5.30 P.M Dr L Forman Cutaneous Manifestations of Viscera Malignancy

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W 1
8 P.M Dr H J G Bloom, Mr D M Wallace, Mr Robert Cox Treatment of Carcinoma of the Bladder

ALFRED ADLER MEDICAL SOCIETY
8 P.M (1, Wimpole Street, W 1) Dr Walter Schindler Indications fo Group Psychotherapy

Friday, 15th

ROYAL SOCIETY OF MEDICINE
5.30 P.M *Epidemiology and Preventive Medicine* Dr N S Galbraith Dr J C McDonald, Flight-Lieutenant D M Miller, Dr M Patricia Jevons, Dr J D Rycroft, Dr R E O Williams Carriers of Penicillin-resistant Staphylococci Outside Hospital
8 15 P M *Radiology* Dr J G Stewart Dr Robert Gibb, Dr K S Holmes, Dr R C S Pointon Clinical Applications of Megavoltage

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr R. W Raven Cancer Cell and Surgery
4 P M Dr J F Goodwin Pulmonary Circulation in Heart-disease

FACULTY OF RADIOLOGISTS, 47, Lincoln's Inn Fields, W C.2
4 30 P.M (Royal College of Surgeons) *Radiotherapy* Dr J S Fulton Dr Richard Doll, Dr F Dudley Hart A Critical Survey of the Value of Radiotherapy in the Treatment of Ankylosing Spondylitis

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C.1
5.30 P.M Mr Maxwell Ellis Nasal Physiology and Pathology

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W C.1
4 30 P.M. Dr P K Thomas Clinical Applications of Electromyography

PLYMOUTH MEDICAL SOCIETY
8 30 P.M (Freedom Fields) Mr R V Cooke Bees in my Bonnet.

Appointments

BARTON, R W A C, M B Lond, D P M physician superintendent, Severalls Hospital, Colchester, Essex

CROSS, R M S, M R C.S ophthalmologist (S H M O), Petersfield school eye clinic

DANIK, J J, Dipl Lwow D P M consultant psychiatrist, Towers Hospital, Humberstone, Leicester

PLATT, J W, B.M Oxon, M R C P, D C.H consultant pædiatrician, Cumberland and North Westmorland area hospitals

STRAUSS, W T, M.D Hamburg, F R F P.S consultant physician, Arbroath Infirmary and Dundee Royal Infirmary

Manchester Regional Hospital Board

CROSS, J R M B Birm, F F A R C.S part-time consultant anæsthetist South Cheshire group of hospitals

HALNAN, K E., M D Cantab, F F R, D M R T consultant radiotherapist, Christie Hospital and Holt Radium Institute, Manchester

ROGERS VINCENT, M B Lpool, D M R D part time consultant radiologist Salford group of hospitals

SMITH, H F, M.B Manc, F R C.S consultant surgeon, Blackpool and Fylde group of hospitals

The Lancet · Saturday 16 January 1960

G.P.I. IN AN OBSERVATION WARD

ROBIN STEEL
M.B Lond., D.P.M.
LATELY SENIOR HOUSE-OFFICER IN PSYCHOLOGICAL MEDICINE,
UNIVERSITY COLLEGE HOSPITAL, LONDON, W.C.1

SYPHILIS is not in fact a "dying disease" (King 1958), but, despite warnings (Harris 1958, Mayer-Gross 1958), parenchymatous neurosyphilis is generally thought to be very rare.

During the eighteen months from April, 1957, to September, 1958, at St Pancras observation ward, 18 cases of general paralysis of the insane (G.P.I.) were admitted. Of these 12 were hitherto untreated. In addition 1 case of juvenile G.P.I. and 2 patients with dementing illnesses and positive Kahns reactions, but negative blood Wassermann reactions (W.R.) and cerebrospinal-fluid (C.S.F.) findings, were admitted. These last 2 patients had recently had intensive antibiotic treatment for respiratory infections, and 1 died of syphilitic aortitis proven at necropsy.

Patients are admitted to the 70-bedded observation ward by the London County Council duly authorised officers and police, usually from central London and north of the Thames, on an order lasting seventeen days. Blood W.R.s and Kahn reactions are taken routinely on admission, and all patients with neurological conditions are examined by the consultant neurologist.

To show the various ways in which cases are still presenting, and to emphasise that clinical examination without serological examination is insufficient to exclude syphilis, brief case-histories of the 12 untreated and 2 recently treated cases are recorded.

Case-reports

Case 1.—A 53-year-old lorry-driver was admitted from a police-station. He was disorientated and confused, and believed he could be saved by Spilsbury. Although all reflexes were increased, his plantar responses were flexor. He had a cerebellar tremor of his left hand. There was no proprioceptic loss or pupillary signs. After treatment with chlorpromazine and penicillin he was transferred to a mental hospital, but he was so upset on hearing a membership tutorial class suggest that he may have "G.I.P.", that he returned to the observation ward. Although not psychotic, he was irresponsible. He had a valid driving licence, and would not consider alternative plans. He remained for a month on a voluntary basis, during which he was well except that he imagined himself to be one of the nursing staff. When he discharged himself he was adamant that he had no general practitioner but used the casualty department of a teaching hospital for this purpose. He had recently had his teeth extracted there for arthritis and malaise.

Case 2.—A senior clerk, aged 51, with a good war record in the R.A.M.C., had been attending his general practitioner for a year with lassitude. Three weeks before admission to hospital he attended a psychiatrist at a teaching hospital, but he failed to respond to tablets and was admitted there for two days. Because of his retardation and delusions of guilt, he was transferred to the observation ward. There were no abnormal physical signs. Mentally he was slow and dejected, believing himself to be doomed. His condition showed no improvement after a full course of penicillin, but a month later, after electroconvulsive therapy (E.C.T.), it was greatly improved. His I.Q. was then 104, and there was no evidence of dementia. He was discharged home and follow-up at the other hospital was arranged.

Case 3.—A 37-year-old Sierra Leone ex-seaman was transferred from a neurosurgical unit where he had spent a week for investigation after an epileptic fit, he had then become overactive. His hæmoglobin was 85%, white blood-cell count 7200 per c.mm., and erythrocyte-sedimentation rate (E.S.R.) 65 mm. in the first hour (Westergren). On admission to the observation ward the only abnormal physical signs were tibial scars. Mentally he was restless, he prowled around and was overactive. After being given penicillin he was found a new job and lodgings, and was discharged greatly improved.

Case 4.—A clerk, aged 47, who had graduated from one of the older universities had been having treatment for migraine at a teaching hospital. He had been remanded for a medical report by a magistrates' court. The prison medical officer regarded him as certifiably insane, and he was admitted to the observation ward from court. Physical examination showed a fine tremor only. Mentally he was euphoric, demented, and unconcerned, his I.Q. was 94. He went to a mental hospital as a voluntary patient.

Case 5.—A 72-year-old Pole had been under the care of geriatricians for seven months. He had had several little strokes in the past six years, and his son and family, who cared for him, had noted that though once he could speak six languages now he could use only his native tongue. He was grossly demented, and he had small irregular pupils and a right-sided mild hemiparesis. He went to a mental hospital on form "A" after treatment.

Case 6.—A man aged 47, a drain flusher, had just been in prison where the doctor regarded him as a psychopath with a social problem, but not as certifiably insane.

He was admitted to the general wards of University College Hospital because the pædiatrician at another hospital, where he had taken his stepson, thought he looked ill. He was febrile (103°F), with a resolving pneumonia, but he also had irregular pupils, ptosis, and an upper-motor-neurone lesion of the left arm. Mentally he was euphoric and demented. Next day, when his behaviour deteriorated and his temperature fell, he was transferred to the observation ward. From there he went to a mental hospital as a voluntary patient.

Case 7.—A single milliner, aged 42 (the only untreated female patient) of Continental extraction, had not worked for six months. She had only just been discharged from a teaching hospital after operative treatment for varicose veins.

She showed fixed irregular pupils, ankle-clonus, and a left extensor plantar response. She had grandiose delusions and was hypomanic and disorientated. She was certified.

Case 8.—A 44-year-old housewife, whose youngest child was educationally subnormal, had for six months been attending a psychiatric clinic with the label of "hypomanic reaction in a woman of low intelligence". She had been a surgical inpatient for assessment of her incontinence.

The only abnormal physical signs were one tibial scar and a right extensor plantar response. Mentally she was overactive and elated, with occasional paranoid fears.

In view of a negative blood W.R. and adhesions in a chest radiograph, her C.S.F. was cultured but there was no growth. There was no other evidence of tuberculosis. Skull radiographs, an electroencephalograph (E.E.G.), blood-count, and E.S.R. were all compatible with G.P.I. She was certified and transferred to a mental hospital.

Case 9.—A Post Office engineer, aged 27, was admitted from a police-station in an excited condition, his personality having changed over the previous ten days. His left pupil was oval and sluggish, and he had diminished reflexes and proprioceptive sensation in the legs, but bilateral extensor plantar responses.

He was manic, he thought he was Christ and must clean up London with a hydrogen bomb. After treatment with chlorpromazine he became quieter and agreed to go to a mental hospital as a voluntary patient

Case 10 —A 38-year-old greyhound attendant had been forgetful for a month, and grandiose for two days He had had an episode, eight years ago, of confusion with twisting of his left arm and mouth, which improved after six weeks' conservative treatment at home He had served on the Continent with the Army Catering Corps during the war

He had irregular, small, but reactive pupils, and his plantar responses were doubtfully extensor Mentally he was glib, euphoric, and disorientated, he claimed to have sold 20,000 pigs at Smithfield He frequently attributed his admission to the observation ward to a head injury caused by falling off his personal elephant in the Australian jungle An E E G showed diffuse abnormalities He was transferred to a mental hospital as a voluntary patient

Case 11 —A 44-year-old Hungarian refugee, whose mother, two siblings, first wife, and two children had been killed in concentration camps, had also been imprisoned himself for three years Shortly after coming to England, eighteen months previously, he had learnt that his second wife had leukæmia, and this, with his inability to find employment or to learn English, produced a severe melancholia He was treated with a course of E C T, vitamins, and euphoriant drugs in the psychiatric outpatient department of a postgraduate institute for eight months He made a good recovery but was forgetful A week before admission to the observation ward his wife died, and he became noisy, agitated, and suicidal

Physical examination was difficult at first because he was so suspicious, but his pupils were seen to be large and unreactive to light No other abnormal signs were found later He was restless, agitated, and preoccupied with mourning ritual He spoke no English, but his friends said his paranoid ideas had ceased

After treatment with penicillin he was seen by a Hungarian-speaking psychiatrist who said the clinical picture was only one of dementia He returned to the care of his relatives and friends

Case 12 —An electrical engineer, aged 54, had come to England from Belgium when he was 13 He had been a good workman but four years previously had begun to steal, and he had been unemployed for the past two years At first he lived on his savings, but he spent these rapidly He then lived for a year on the charity of his neighbours, becoming more eccentric and grandiose, and going to the police-station to say that he had won two Nobel prizes

He had fixed small pupils, slurred speech, tremor of his tongue, very brisk reflexes, clonus, and extensor plantar responses He was euphoric, with delusions of grandeur

He was certified and transferred to a mental hospital

The table shows the findings in the C S F and blood in these 12 cases before treatment All were treated with penicillin by injection as soon as the diagnosis was made, and where possible a course of 28 million units was given No side-effects arose No other antisyphilitic drugs were used (Kofman 1956)

FINDINGS IN C.S F AND BLOOD IN 12 UNTREATED CASES OF G P I

Case *no*	C.S F				Blood	
	White cells (per *c mm*)	*Protein* (mg per 100 ml)	Lange curve	W.R	W R.	Kahn
1	13	150	5 5 5 5 5 5 5 5 4 4	+	+	+
2	23	70	5 5 5 3 3 1 0 0 0 0	+	+	+
3	30	50	5 5 5 4 3 2 0 0 0 0	+	+	+
4	45	100	5 5 5 3 1 0 0 0 0 0	+	+	+
5	6	130	5 5 5 5 4 2 1 0 0 0	+	+	+
6	32	90	5 5 5 5 3 1 0 0 0 0	+	+	+
7	32	110	5 5 5 5 5 5 4 4 3 2	+	+	+
8	70	70	3 4 5 4 2 1 1 1 0 0	+	−	+
9	13	50	5 5 4 3 1 0 0 0 0 0	+	+	+
10	5	40	5 5 5 4 2 1 0 0 0 0	−	+	−
11	5	65	5 5 5 4 3 2 1 0 0 0	+	+	+
12	15	70	5 5 5 5 3 2 1 0 0 0	−	-	+

The following 2 cases had been treated before admission to the observation ward

Case 13 —A 46-year-old Cypriot had been in England for three years After a fall from a bus, nine months previously, his condition began to deteriorate He complained of difficulty in walking, but was sent away from a postgraduate teaching hospital as a hysteric Three months earlier he had been in another observation ward after threatening suicide by trying to climb on the Underground track His pupils reacted sluggishly, he was sullen, negativistic, and deluded

After the diagnosis of G P I was confirmed, he was transferred to a postgraduate teaching institute There, despite penicillin, tranquillisers, E C T and barbiturates intravenously, and although some of the staff spoke his own language, he became worse and refused food As he was unfit to be a non-statutory patient, he was sent home and seen there by the duly authorised officer Since the diagnosis was in no doubt, he was transferred to a mental hospital under certificate without further investigation

Case 14 —An Irishman, aged 59, had been a commissionaire and was now a waiter In 1946 he attended the venereal-disease department of a teaching hospital, where his W R was found to be positive and he was given one injection of penicillin. He failed to return for further treatment, although he knew that, as well as his gonorrhœa which was cured, he had a " touch of the pox " He entered another teaching hospital in 1948 with lymphadenopathy, and a biopsy diagnosis of reticular sarcoma was made According to their postal follow-up inquiry, he was well in 1958

Towards the end of 1957, because of failing vision he went into another hospital A diagnosis of neurosyphilis was made, and he was transferred to a postgraduate institute for treatment The C S F contained 16 white cells per c.mm protein 125 mg per 100 ml Lange curve 5 5 5 5 5 3 3 3 3 3 His neurological signs were unchanged, but he began to have paranoid ideas He was seen after discharge by the psychiatrist, and accepted an offer of treatment as a voluntary patient at a mental hospital While this was being arranged he travelled to Dublin to implore the police to cease accusing him Having failed to stop the hallucinations, he returned to London and was admitted to the observation ward

He had optic atrophy, ptosis, irregular pupils, absent ankle-jerks, and diminution of proprioception, and a left extensor plantar response He was haunted by horrible accusing hallucinations, and, apart from the accompanying depression, he showed slight dementia

As the original voluntary-patient vacancy was for the next day, he was then transferred to the mental hospital He discharged himself against advice, and he was readmitted to the observation ward eight days later in an unchanged state The blood W R was negative and the Kahn reaction positive The C S F contained 1 white cell per c mm , protein 50 mg per 100 ml Lange curve 5 5 5 5 4 3 1 0 0 0 He was returned to the mental hospital, under certificate, having started another course of penicillin

Discussion

Neurosyphilis is probably more common than is assumed Hughes (1959) described 10 recent untreated cases presenting to a neurosurgeon Only cases which fail to reach general or mental hospitals, or do not get effective treatment, will be seen in an observation ward Routine serological examination obviously still has a place on economic as well as humanitarian grounds Psychotic episodes may arise in treated cases with a resolving or normal C S F , even after adequate antisyphilitic therapy, and a more careful follow-up or a warning to the near relatives might reduce the interval before they receive psychiatric treatment

The National Health Service seems very well suited to the needs of the peripatetic ex-patient who has no relatives to remind him to attend a follow-up clinic, for if he changes his general practitioner his new doctor should receive his record card, including any letters from hospital Unfortunately, however, few of these patients bother to register with a doctor, and they will probably continue to be treated as temporary patients, or at casualty departments where their past is unknown

Summary

18 cases of general paralysis of the insane, were admitted to one observation ward within eighteen months

The case-histories of 12 untreated and 2 recently treated patients are recorded to show the variable clinical picture

Syphilis is by no means a dying disease, and routine serological examination is important

I should like to thank Dr E W Dunkley for his permission to publish and his criticism

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TREATMENT OF ADVANCED CARCINOMA OF THE BREAST BY BILATERAL OOPHORECTOMY AND PREDNISONE

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FOR many years the production of hormonal imbalance has been used in the treatment of advanced breast cancer In 1896 Beatson suggested therapeutic castration and Treves and Finkbeiner (1958) review the historical background At this hospital, owing to the short-lived remissions following bilateral adrenalectomy and oophorectomy and the difficulty of maintaining these patients in electrolyte balance, it was decided to try the effect of bilateral oophorectomy together with corticosteroid treatment Reports on similar methods have already been given by Nissen-Meyer (1957) and Lemon (1959), and the present report concerns the treatment of 82 patients with advanced carcinoma of the breast

Material and Methods

All the patients selected had advanced carcinoma of the breast, and at the time of surgical castration were grouped as stage-IV cases Most patients had been treated previously by radical surgery and radiotherapy Several patients had hormone treatment when their metastases were first noticed, and it was not until the remissions from this treatment were exhausted that bilateral oophorectomy was undertaken. A smaller group of patients seen for the first time when their disease was already very advanced were initially treated by oophorectomy and prednisone The ovaries were removed either at Addenbrooke's Hospital or at one of the smaller hospitals in the area served by the Addenbrooke s Radiotherapy Department Prednisone 10 mg b d. was started as soon after surgery as practicable—usually within 48–72 hours

The response to treatment was evaluated by careful clinical follow-up, subjective and objective improvement were noted, and tumour regression also measured wherever possible The quality of remission was considered to be no less, if not more, important than the length of survival following operation

A response was considered *satisfactory* if there was evidence of objective and subjective improvement enabling the patient to lead a relatively normal life again Such a response was considered terminated when further palliative measures were necessary in order to prolong useful life

A response was classed as *unsatisfactory* if improvement was purely subjective and objective improvement could not be demonstrated

To try and find out whether any features could be used for prognosis, the quality of the response was related to (*a*) the menopausal status of the patients, (*b*) the previous response to hormone therapy, (*c*) the presence or absence of ovarian metastases, (*d*) the length of history prior to oophorectomy

The question of ovarian cortical stromal hyperplasia was also considered, but the changes detected in the sections could not be assessed by a sufficiently quantitative method to give any information of value The presence of widespread liver metastases had been noted at operation in a few patients

TABLE I—MENOPAUSAL STATUS IN RELATION TO RESPONSE

Menopausal status	No of patients		Satisfactory response	
	" Primary "	Advanced	" Primary "	Advanced
Premenopausal	9	43	6	17
Menopausal	1	8	0	2
Postmenopausal	0	10	0	4
No information	6	5	3	1
Totals	16	66	9	24

Results

Of the 82 patients treated, 16 were in the group of " primary " oophorectomy, and, of these, 9 had a satisfactory response 66 were treated after other forms of therapy had failed, of these, 24 had a satisfactory response with definite objective improvement, and were able to lead an active and useful life following operation, the remaining 42 patients, although many survived for many months, were considered to have had unsatisfactory responses and continued to need frequent hospital care and further palliative treatment

Of the 16 patients treated in the first instance by castration 9 were considered to have a satisfactory response and 7 an unsatisfactory response This group was a little more difficult to assess as they had not been under observation for any length of time before operation.

Menopausal Status

The relation of the meopausal status to the type of response is apparently not important in either group of patients treated (table I) The menopausal status was, however, assessed at the time of primary treatment of the original lesion, and thereafter some considerable time elapsed before oophorectomy, and the situation was often further modified by the use of hormones

Previous Hormone Therapy

Hormone therapy had been prescribed before oophorectomy in 42 cases, but the response to this therapy was not always easy to assess, especially as the patients had been under the care of different doctors The response to hormone therapy was classified as positive (i e., the lesion classified as hormone-dependent), negative, or doubtful In the last category the changes in the patient's condition following hormone therapy were too indefinite to allow their lesions to be classified as " hormone-

TABLE II—HORMONE DEPENDENCE IN RELATION TO RESPONSE

Hormone dependence	Unsatisfactory response	Satisfactory response
Positive	10	10
Negative	5	1
Doubtful	11	5
Not tried	16	8
Totals	42	24

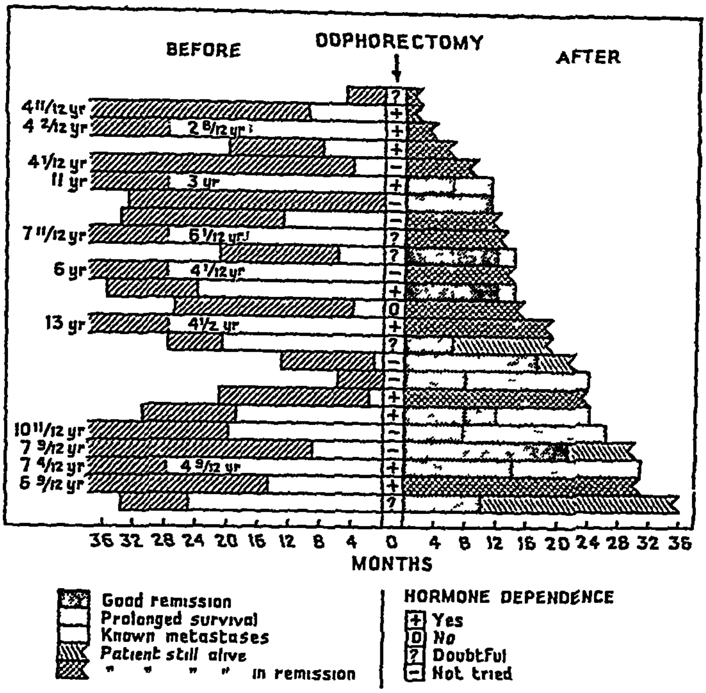

Fig 1—Satisfactory responses of patients with advanced carcinoma of breast to bilateral oophorectomy and prednisone

dependent" In order to avoid bias, the response to hormone therapy was always assessed before the response to oophorectomy was known In the satisfactory group 10 out of 16 patients were considered to have hormone-dependent lesions and in the unsatisfactory group 10 out of 26 (table II)

Ovarian Metastases

Metastases in the ovaries were found in 10 of the 44 specimens examined The degree of destruction of ovarian tissue varied enormously, and the response to operation seemed to be unrelated to these findings (table III)

Length of History Before Oophorectomy

In both the satisfactory and the unsatisfactory groups patients were known to have had the disease for many years The response to castration was apparently unrelated to the previous duration of the disease (figs 1 and 2)

TABLE III—OVARIAN METASTASES IN RELATION TO RESPONSE

Histological findings	No of specimens	Satisfactory response
Metastases present	10	4
No metastases	34	18
Not examined	38	11
Totals	82	33

Liver Metastases

Extensive metastases in the liver were noted at operation in 7 patients, and 2 of these subsequently had very satisfactory remissions

Other Metastases

The time from the first treatment to the first exacerbation of the disease was known in 60 patents Bone metastases were the first to develop in 28 patients, and 8 of these were subsequently classified as having had a good response to oophorectomy Of the 32 patients who first presented with soft-tissue spread 13 responded satisfactorily

Survival-time

The average survival-time for the advanced patients in the satisfactory group was 16 5 months, as against 6 months for the other advanced cases (fig 3) In the "primary" group the patients with a satisfactory response had an average survival of 16 months, and the others 3 months The results are summarised and the quality of remission together with the survival-time for each patient are shown in figs 1, 2, and 4

Case-records

The following 3 case-records illustrate the quality and the length of survival in a really satisfactory remission

Case A—A childless married woman of 42 who noticed a lump in her breast in June, 1949 6 months later she reached hospital and had a radical mastectomy for a stage-II carcinoma of the left breast. The histologist reported a mucoid papillary carcinoma of the breast A radical course of postoperative X-ray therapy was planned for the patient, but this treatment was never completed as she developed infective jaundice She remained in good health for five years, after which lung metastases developed in July, 1955 She was treated with testosterone propionate intramuscularly and obtained a good clinical remission for a year, although there was no improvement in the appearance of the metastases in chest X-ray films At the end of the year her condition worsened and radiography showed extension of the chest metastases

She had a bilateral oophorectomy in September, 1956, after which she had a temporary improvement of six weeks' duration. Owing to a misunderstanding prednisone was not administered until 8 weeks after oophorectomy, when she was

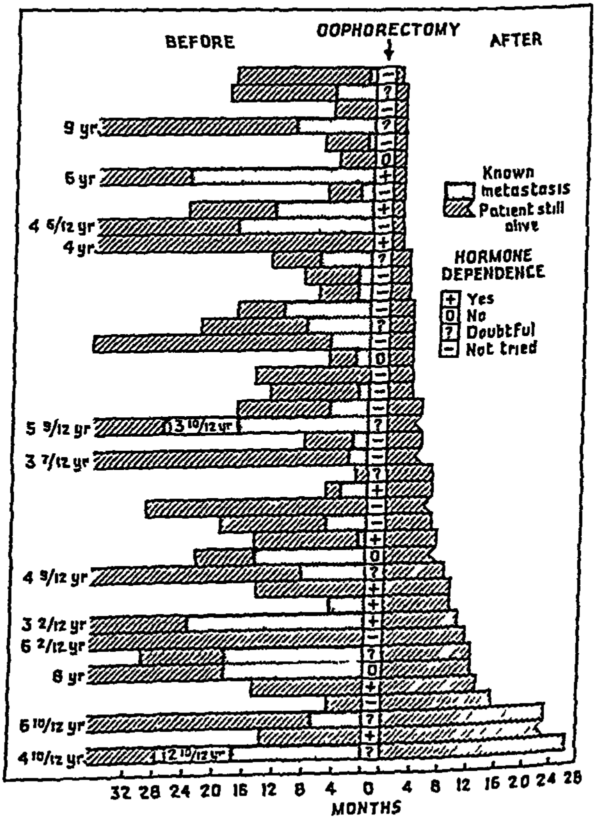

Fig 2—Unsatisfactory responses of patients with advanced carcinoma of breast to bilateral oophorectomy and prednisone

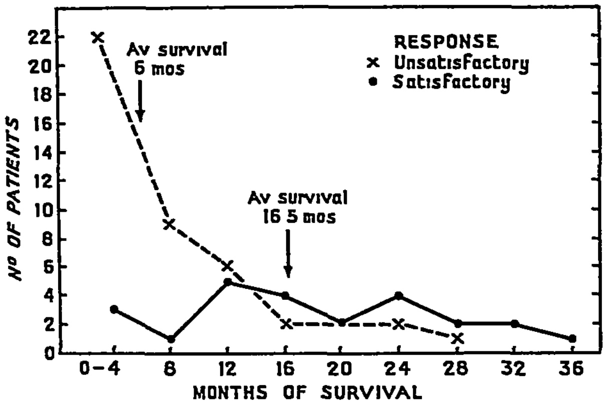

Fig 3—Distribution of satisfactory and unsatisfactory responses in relation to survival-time

again distressed and was very dyspnœic at rest Prednisone 20 mg b d was then administered Metastases in her chest steadily improved, and after 6 months the prednisone was reduced to 10 mg b d

In the 33 months since oophorectomy her condition has continued to improve, and the last chest film shows no evidence of metastases She is a little " moon-faced " but is able to lead a normal life X-rays of the chest are shown before and after treatment in fig 5

Case B —A married woman of 47 with 1 child had had a lump removed from her right breast 12 years previously by local excision In May, 1955, she was referred with " sciatica ", and radiography showed multiple metastases throughout her pelvis and spine with collapse of D11 vertebra She also had a clinically malignant local recurrence of a breast tumour

She was treated with palliative doses of X rays to her bones and injections of testosterone propionate, and had a fair remission with almost complete relief of pain This remission lasted about 2 years, after which pains returned She was admitted in October, 1957, with almost complete paraplegia due to further vertebral collapse

Bilateral oophorectomy was performed and in October, 1957, prednisone 10 mg b d was started 6 days post-operatively

Since then her condition has steadily improved, and the only residual sign of paraplegia is a slight weakness in the left leg, which does not prevent her from leading a normal life and running her home Her weight has increased a stone since her operation, but this does not worry her Radiography shows little change since the oophorectomy, but there is some sclerosis of the metastases

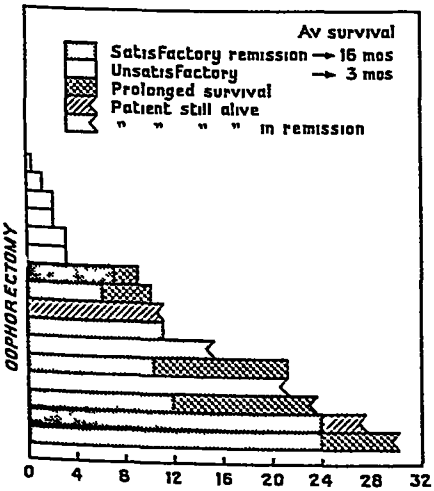

Fig 4—Response of patients with advanced carcinoma of breast to primary treatment with bilateral oophorectomy and prednisone

Case C —A married woman with 3 children first attended hospital in October, 1954 For 2 years she had noticed a lump in the left breast, and a lump had been found in the right breast 6 months previously There was a 4-month history of backache Clinically there was a large ulcerated scirrhous carcinoma of the left breast with fixed axillary and supraclavicular glands On the right the carcinoma and the axillary nodes were mobile There were widespread skin metastases over the trunk, and bone-marrow aspiration showed numerous malignant cells As the patient refused bilateral adrenalectomy, intramuscular testosterone propionate was given, and the patient had a good remission until July, 1956 At this time the skin nodules were increasing in size and abdominal ascites was developing There was slight improvement after the testosterone injections were stopped, but by May, 1957, ascites was severe, and bilateral oophorectomy was performed on May 24 Prednisone 10 mg b d was started 5 days after operation, and the patient improved and remained well until September, 1958, when ascites once more became a problem Intraperitoneal gold in October, 1958, gave another short remission until February, 1959, when the patient started to deteriorate rapidly, she died in April, 1959, some 4½ years after attending hospital with a very advanced neoplasm with bone-marrow involvement.

Discussion

Previous critical assessments of hormone treatment of advanced carcinoma of the breast have nearly all reported 30–40% of good results (see Treves and

Fig 5—Case C (a) 1 month before oophorectomy, (b) 30 months after oophorectomy

Finkbeiner 1958) It seems that 30–40% of patients are likely to have "hormone-dependent" tumours, but the type of hormone treatment which gives the most satisfactory results is not yet clear, and as yet there is no method of determining which patients are likely to have "hormone-dependent" tumours

The present series indicates that patients who have had a remission following androgen treatment are likely to get a further remission from oophorectomy and prednisone However, failure to respond to androgen does not necessarily indicate that oophorectomy will fail, and as yet we have no method of selecting patients who are likely to respond satisfactorily to oophorectomy

The advantages of bilateral oophorectomy followed by administration of prednisone are, firstly, the comparatively minor nature of the operation with an average stay in hospital of 10 days, and, secondly, the prednisone besides helping to suppress the tumour imparts a feeling of well-being In addition, administration of low doses of prednisone does not require much supervision Operation is necessary because X-ray castration does *not* completely stop ovarian function A patient in pain preoperatively who responds to operation will *probably* be completely relieved of pain as soon as she has recovered from the anæsthetic The *only* disadvantage of this treatment seems to be the increase in weight due to fluid retention, but this is an embarrassment to only a minority of the patients

We do not know how the prednisone acts Through the pituitary it may suppress adrenal function, or it may act directly on the tumour Experience has indicated that 20 mg daily is about the optimum dose, and we think it likely that its action is not simply that of a euphoriant

Summary

82 patients with advanced carcinoma of the breast were treated by bilateral oophorectomy and administration of prednisone

16 patients were treated by "primary" oophorectomy, and 9 of these had a satisfactory response their average survival-time was 16 months, compared with 3 months for the 7 patients in the unsatisfactory group

66 patients were treated when remissions by X-ray and/or hormone therapy were exhausted 24 of these had a satisfactory response with an average survival-time of 16 5 months, compared to 6 months for the 42 other patients Of 16 patients showing a satisfactory response, 10 were found to have hormone-dependent tumours, whereas of 26 showing an unsatisfactory response only 10 were considered to have hormone-dependent tumours

The menopausal status, the presence of ovarian metastases, and the length of history before oophorectomy or liver involvement appeared to be of *no* definite prognostic significance

Bilateral oophorectomy and administration of prednisone are useful in the treatment of patients with very advanced carcinoma of the breast

We would like to thank our many colleagues in this area who have directly and indirectly helped with this project, and Prof J S Mitchell for his helpful discussion of this paper

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TREATMENT OF INGUINAL HERNIÆ

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St Thomas's Hospital has long been associated with the medical care of members of the Metropolitan Police Force As a result it has been possible to achieve a high follow-up rate after these patients leave hospital

The results of operations for inguinal hernia on members of the Metropolitan Police were reviewed by N R Barrett in 1934, and by A G McPherson in 1943, on behalf of Sir Max Page (1934, 1943)

In view of the new techniques introduced in recent years it was thought that a further review might be of value An attempt was made to examine all Metropolitan policemen, totalling 266, who had been operated upon for inguinal hernia between 1945 and 1954, the follow-up period being between 12 and 4 years

The great majority presented themselves for examination 23 who had retired from the Force and lived far away were seen by their own doctor, a few were unresponsive and had to be visited in their own homes All those included in this series were medically examined Postal questionnaires were not used

Findings

Of the 266 patients, 5 had died of intercurrent disease and 5 were untraced (2 in the U K , 1 in Canada, 1 in the U S A, and 1 in Australia)

The 256 who were successfully followed up had an average age at operation of 40 years (range 21–60)

Inguinal herniæ operated on numbered 335 (i e , 79 had bilateral herniæ) Recurrences totalled 48 (14 3%) The recurrence-rate according to type of hernia is shown in table I Tables II–IV show the recurrence-rates for indirect, direct, and recurrent herniæ related to the types of operations

No definite reason was found for the choice of repair operation It appeared to depend on the type of operation in favour at the time, and on the particular surgeon's beliefs, except that herniotomy and plication was reserved for very minor weakness of the posterior wall, and that the Bassini operation was not done on the bigger direct herniæ.

TABLE I—RECURRENCES IN 335 HERNIÆ

Type	No	Recurrences
Indirect	204	29 (*14 2%*)
Direct	94	17 (*18 3%*)
Recurrent *	37	3 (*8 1%*)

* First operation at St Thomas's Hospital in 28, elsewhere in 9, cases

TABLE II—RECURRENCES IN 204 INDIRECT HERNIÆ

Operation	No	Recurrences
Herniotomy	54	9 (*16 7%*)
Herniotomy + plication of *transversalis fascia*	13	2
Bassini	26	8 (*30 8%*)
Bassini + Tanner slide	10	2
Gallie	44	3 (*6 8%*)
Floss-silk darn *	12	2
Bloodgood	3	0
Nylon darn	40	2 (*5%*)
Others	2	1
Total	204	29 (*14 2%*)

* Method used by one surgeon only

TABLE III—RECURRENCES IN 94 DIRECT HERNIÆ

Operation	No	Recurrences
Herniotomy + plication	3	0
Bassini	12	3
Bassini + slide	5	1
Gallie	28	6 (*21 4%*)
Floss-silk	6	2
Bloodgood	5	0
Nylon darn	32	4 (*12 5%*)
Others	3	1
Total	94	17 (*18 3%*)

TABLE IV—RECURRENCES IN 37 RECURRENT HERNIÆ

Operation	No	Recurrences
Herniotomy	2	0
Bassini	4	1
Bassini + slide	1	0
Gallie	5	1
Bloodgood	1	0
Nylon darn	18	0
Others	6	1
Total	37	3 (*8 1%*)

These results compare with

Barrett, 1934 —206 cases treated predominantly by Bassini or Foster technique, with a recurrence-rate of 20% for indirect herniæ and 25% for direct herniæ.

McPherson, 1943 —174 cases, treated mainly by herniotomy or Gallie's operation, with a total recurrence-rate of 14 9%—indirect 12%, direct (17 cases) 35 3%

Discussion

The criterion of a recurrent hernia was considered to be the presence of an expansile cough impulse It has not seemed reasonable to defer diagnosing recurrent hernia until this caused disability indeed, in this series over 10% of recurrences were unnoticed by the patient Asymptomatic recurrences make reviews which are not based on physical examination liable to error

The persistence of a high recurrence rate is disturbing, and we feel that this series reveals features which could point the way to better results

Type of Operation

Case-histories were inadequate to correlate the type of operation with the state of the posterior wall of the inguinal canal Where, however, a repair has been considered necessary, the best results appear to follow the nylon-darn, now commonly used in place of the Gallie, and the Bloodgood types of techniques Unfortunately there were too few of the latter to allow a firm conclusion to be made The Bassini operation has been associated with a high incidence of recurrence at this hospital, but the figures are too small to determine whether the results varied with the suture materials used.

Priority

Inguinal herniæ are often relegated to the end of the list and are too often done by inexperienced operators without adequate supervision The recurrence-rate for indirect herniæ operated on by housemen was 20%, compared with 9% by registrars

The high incidence of recurrence following herniotomy alone can be partly ascribed to bad choice of operation, as many as a third being done on patients between the ages of 40 and 59 In this series simple herniotomy has a low recurrence-rate up to the age of 39, after which it rises steeply

It is also difficult to escape the conclusion that the remarkable results obtained on recurrent herniæ are partly related to the extra care which is called forth by these herniæ.

Further information acquired from this series confirms that postoperative sepsis is associated with an increased recurrence-rate, and that neither simultaneous repair of bilateral herniæ nor ambulation during the first postoperative week influences recurrence-rate Almost all recurrences were diagnosed within four years of operation, the majority showed themselves by the end of the first year

The results did not show an increasing liability to recurrence with increasing age of the patient, but "invisible" factors were at work here for example, the younger patients with the simpler herniæ were mainly operated on by younger surgeons

There was 1 sinus following the nylon darn repair

It was not possible to determine whether prophylactic postoperative administration of antibiotics or sulphonamides influenced the sepsis-rate

Conclusion

The results of this review are disappointing Being the unselected results of a number of different surgeons, they probably represent the state of affairs in most hospitals where the treatment of herniæ is given similar priority

Greater attention to the care of these patients is likely to improve results. The final decision as to which operation should be performed should be made when the tissues are exposed at operation, and only by someone with experience

The nylon darn and Bloodgood types of operation have given good results Simple herniotomy for patients with a sound posterior wall gave low recurrence-rates up to the age of 39 The Bassini operation, although apparently successful in certain hands, does not appear to give good results at this hospital

Our thanks are due to the surgeons at St Thomas's Hospital for permission to carry out this investigation, and to the staff of the Medical Branch, Scotland Yard, for help in tracing the patients

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LEISHMANIASIS ACQUIRED BY CONTAGION

A CASE OF MARITAL INFECTION IN BRITAIN

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THE transmission of all forms of leishmaniasis depends ordinarily upon phlebotomus sandflies We owe our freedom from the infection in this country to our climate, which does not suit the insect vectors, and to the absence of any reservoir of infection in the population or in animals The occasional cases which we see originate elsewhere—most of them are examples of the so-called oriental sore, and the diagnosis is readily made when the patient is known to have come from a part of the world where this disease occurs A knowledge of geographical pathology and of the symptomatology of exotic diseases is becoming more and more important as travel becomes easier, faster, and more necessary, and the diagnostic importance of taking an accurate history of patients' oversea journeyings is obvious

The American Geographical Society's (1954) map of the world distribution of leishmanial infections shows that *cutaneous leishmaniasis* (oriental sore) occurs in parts of Europe, Africa, and Asia It is found in the coastal belt of the countries of the whole Mediterranean basin, across Turkey to the Caspian Sea, down through Iraq to the Persian Gulf, across Iran, Afghani-

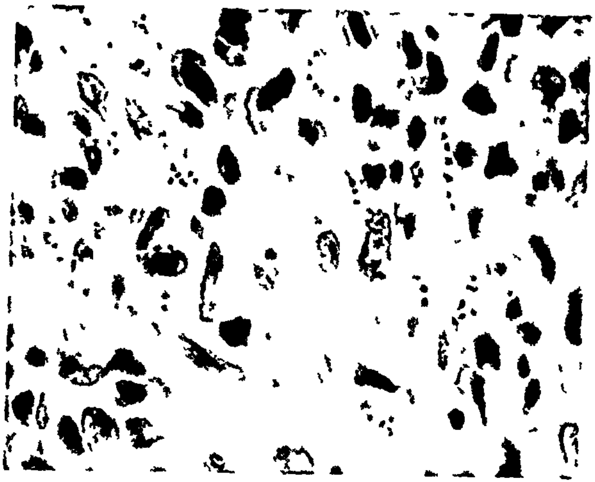

Fig 1—Biopsy of vulvar lesion the leishmanias in the macrophages of the inflammatory exudate are easily seen (Hæmatoxylin-eosin, ×600)

stan, and Turkistan, across Pakistan and northern India, and in Ceylon It occurs in West Africa from the Gambia to the Cameroons, and in East Africa—particularly in Ethiopia Occasional cases have been recognised in other parts of West and East Africa, in Malaya, and in various parts of eastern Asia Isolated cases have also been reported nearer Britain, in Portugal and northern Spain

It is not proposed to refer particularly to *visceral leishmaniasis* (kala-azar) or to *American leishmaniasis* in this paper It may be noted, however, that the geographical distribution of visceral leishmaniasis is a good deal wider than is usually realised, and yet overlaps remarkably little with that of oriental sore An account of leishmaniasis in all its forms is readily accessible in *Manson's Tropical Diseases* (Manson-Bahr 1954), and only some aspects relevant to the cases reported in this paper will be mentioned here

Cases of cutaneous leishmaniasis have been reported in Britain from time to time, and particularly since the late war (Conrad et al 1950, Howell 1957, and others, including cases shown at society meetings, and particularly at the Section of Dermatology of the Royal Society of Medicine) The patients have usually been visitors or immigrants from areas where the disease is endemic From the geographical summary given above it may be seen that some of these areas are commonly enough visited by British businessfolk or holidaymakers, the diagnosis of cutaneous leishmaniasis is worth considering when any patient with an indolent skin lesion has been in such parts The length of stay in an endemic area before infection takes place need be no longer than the few moments taken by a sandfly to feed

The protozoon which causes leishmaniasis was first recognised in a soldier who had come home to this country from India

Leishman (1903) found the organism, in 1900, in smears from the spleen of this man, who had died of kala-azar in the Royal Victoria Hospital in Netley, Hampshire The patient had contracted the disease during service in Dum Dum, the station in Bengal which gave the disease one of its names Publication of Leishman's (1903) observation led Donovan (1903) to record his own independent discovery of the organism, which he had found in Madras in 1903 in smears from the spleens of three patients at necropsy and of one living patient It is appropriate that the names of these two men are coupled in the common designation of the parasites as Leishman-Donovan bodies and in the name of the most important species, *Leishmania donovani* Wright's (1903) discovery of the causative organism of oriental sore, now known as *L tropica*, followed shortly afterwards The other main varieties of *Leishmania* are *L infantum*, which causes visceral leishmaniasis of children on the Mediterranean littoral, and *L brasiliensis*, the cause of American leishmaniasis In addition, mention must be made of *L canis*, which causes leishmaniasis in dogs, particularly in Mediterranean lands but also elsewhere—the infection has, for instance, been found in dogs in the region of Paris (Guilhon 1950) and in Brittany (Guilhon and Loge 1950) It has been suggested that canine leishmaniasis may be a reservoir for human infection There is some doubt whether all these named species of *Leishmania* really qualify to be considered as specifically distinct from one another

The main purpose of this paper is to report a case of leishmaniasis which is unprecedented in that the patient had never been out of the British Isles before she acquired her infection Her case was also remarkable in that the lesion, which was on the vulva, was almost certainly the result of direct contagion her husband had a symptomless recurrence of visceral leishmaniasis contracted several years earlier in north-eastern Africa As the clinical and laboratory management of her case was bedevilled by a series of avoidable mistakes, before the correct diagnosis was made, it may be politic to make known that the investigations and treatment were carried out in hospitals and laboratories which are not in London, and that she developed the lesion in 1955 Both patients know the full circumstances of the mistakes made, and they and the doctors concerned have encouraged publication of this account

Case-records

A woman, aged 38, noticed a small, rather itchy papule a little behind the vaginal orifice and to one side of the midline As it was enlarging she went to her doctor—her husband's brother—a month later The lesion was then a shiny, purple, dome-shaped nodule, a centimetre in diameter, painless, and with a small, central excoriation which the patient attributed to chafing by sanitary towels Nothing was done about the lesion at that time A month later it was almost twice as large the central erosion had become a round, sharply outlined, steep sided but quite shallow ulcer, about a centimetre across, with a grey base There was now a group of moderately enlarged, firm, painless, lymph-nodes medially in the groin on the same side Her doctor diagnosed primary syphilis although he had never seen a chancre at that time

Blood for a Wassermann reaction was sent to a laboratory where, it so happened, it was still the practice for the entire Wassermann procedure to be carried out by the pathologists Unfortunately, the senior registrar whose turn it was to do the Wassermann tests had no previous experience of complement-fixation techniques, and as he had just been newly appointed to his job he did not like to admit to this gap in his training It has become clear that in this patient's case he must have either misconducted the test or misinterpreted its result, which was reported to her doctor as positive

The patient was then seen by a gynæcologist, who agreed that the lesion could be syphilitic and recommended appropriate treatment He did in fact say that the Wassermann reaction should be repeated and a Kahn test done as a confirmatory precaution before treatment was started, but this advice was overlooked and a month's course of penicillin was begun without further ado The patient had never had treatment with penicillin before During the last few days of the course she felt unwell she became somewhat feverish and developed joint pains and an erythematous rash on her face and body The significance of this syndrome was not realised at the time, but it was almost certainly a reaction to penicillin, to which she is now known to have become sensitive Her Wassermann reaction becomes positive whenever a penicillin reaction is provoked (her Kahn-test result is negative at all times) This may explain why the Wassermann reaction at the end of the month's course of penicillin was reported (this time, by chance, in a different laboratory) as " + ± ", the Kahn test, done then for the first time, was negative.

Although by then the local lymphadenopathy had disappeared the vulvar sore was larger than before the course of penicillin. For some reason which is no longer clear a darkfield examination was carried out now, for the first time, it was reported as negative.

Both the patient and her husband denied having had sexual intercourse with anyone else. As the husband had no genital lesions and his Wassermann and Kahn reactions were negative his wife's truthfulness seemed to be in doubt, he left home. Fortunately, it was at last beginning to be realised that there was something inconsistent between the clinical findings and the supposed diagnosis of syphilis. Biopsy of the ulcer was therefore carried out, five weeks after the end of the course of penicillin and eighteen weeks after the patient first noticed the lesion.

The sections showed a chronic inflammatory reaction in the dermis, nondescript for the most part but with a small area in which typical Leishman-Donovan bodies were readily recognised within macrophages (fig 1). Their presence was confirmed in stained films of exudate from the ulcer (fig 2), and they were also well demonstrated by darkfield examination. When the technician who had been entrusted with the first darkfield examination was shown the leishmanias in the later preparation he recognised at once that he had seen them in the earlier specimen. He explained that he had not drawn anyone's attention to them because he had only been told to look for treponemas. Attempts were made to cultivate the organism from fluid obtained by puncture of the unbroken skin over the periphery of the lesion. they failed because of bacterial contamination.

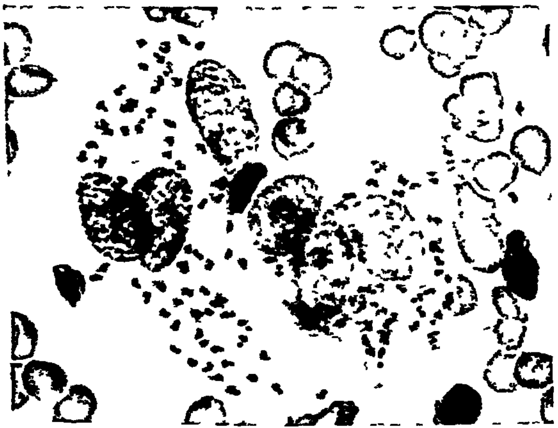

Fig 2—A group of leishmania-laden macrophages in a film of exudate from the vulvar lesion (Leishman's stain, ×900)

As the patient had never been out of the British Isles it was necessary to consider various seemingly unlikely ways by which she could have become infected. There was no immediately obvious solution of this mystery, although all sorts of possible sources of infected vectors were looked for in her environment. By this time it had been possible to get in touch again with her husband, who had gone abroad. he returned home at once with the answer, which unwittingly he had all along possessed, in the form of a history of kala-azar. He had contracted kala-azar while on service in the Sudan, Ethiopia, and Uganda in 1941 or thereabouts. This had been only erratically treated, owing to the exigencies of the times and of his work, and, later, of detention as a prisoner-of-war. The drugs used were probably antimony potassium tartrate and ethylstibamine ('Neostibosan'). By 1944 he was pronounced cured, only to develop typical post-kala-azar dermal leishmaniasis a year later. This in its turn cleared up on treatment with pentamidine isethionate ('Lomidine'), and from then onwards he was free from all symptoms. He married in 1953, eight years later. His wife's leishmanial ulcer developed in 1955, two years after their marriage.

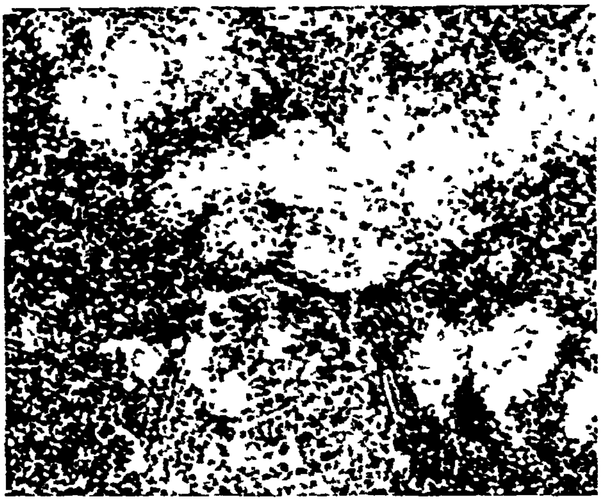

Fig 3—Focal histiocytosis in lymph-node biopsy specimen from the husband of the patient whose infection is illustrated in figs 1 and 2. (Hæmatoxylin-eosin, ×150)

Although at this time he was completely symptomless and for ten years had been aware of nothing amiss with his health, examination showed that the tip of his spleen was palpable four centimetres below the costal margin, his liver was palpable a centimetre below the costal margin, and there was generalised lymph-node enlargement. It seems likely that a complete physical examination instead of the perfunctory inspection of his genitalia at the time when his doctor looked for evidence of syphilis could have led to a prompt appreciation of the true condition of his health and of the nature of his wife's ulcer. When examined he was afebrile. The serum-protein levels were normal. Napier's formol-gel test and the urea-stibamine test were negative. Apart from slight granulocytopenia his blood was normal. The marrow was not examined. Biopsy of an axillary lymph-node showed many discrete, small foci of histiocytosis (fig 3). it was evident that the histiocytes contained minute particles, and at higher magnifications these were clearly recognisable as leishmanias (figs 4a and b). They were well seen in films of fluid from the node, and they were successfully cultivated in "N.N.N." (Novy, MacNeal, and Nicolle medium), in which typical flagellate forms ("leptomonads") developed abundantly within five days on incubation at 22°C. He was treated with pentamidine isethionate (0.2 g intravenously daily for ten days). A month later there was no detectable clinical abnormality, and this is his present state. Before the course of treatment attempts were made repeatedly but unsuccessfully to demonstrate leishmanias in his urine, prostatic secretion, and semen.

The woman's lesion healed satisfactorily when she was given a course of urea stibamine (0.2 g intravenously daily for ten days), it has not recurred (January, 1960). She and her husband have re-established their home and have had their first child, which was born uneventfully eighteen months after cure of the ulcer.

Discussion

Clinicopathological Management

There is no need to discuss the reasons for the mistakes in the investigation and management of the woman's case. Although it is understandable how medical training nowadays might be completed without the student having an opportunity to see a primary syphilitic chancre, it is disquieting that any doctor could consider a single positive report of a single serological test as adequate grounds for telling a patient and her husband that she had syphilis, with all the potential implications and consequences. It is unfortunate that the gynæcologist should have prescribed treatment for primary syphilis without asking

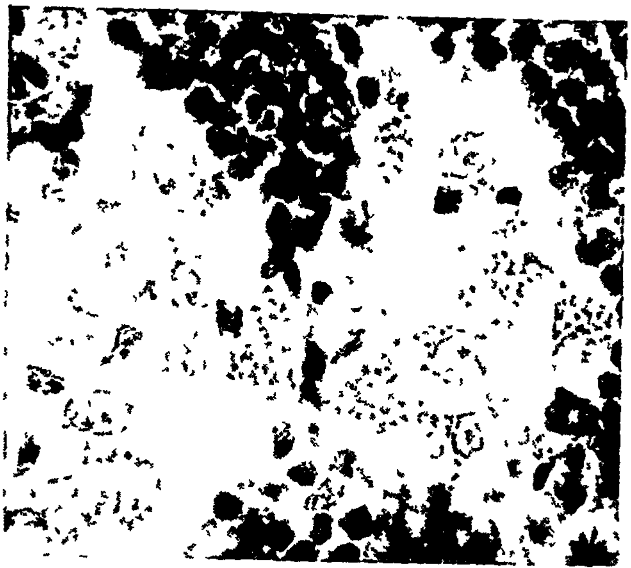

Fig 4a—Higher magnification of a field like that in fig 3 (same preparation) the leishmanias can be seen in the pale cytoplasm of the histiocytes (Hæmatoxylin-eosin, ×650)

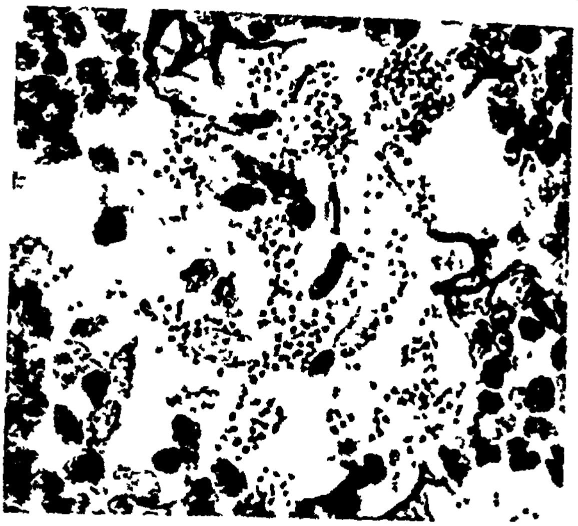

Fig 4b—A field comparable to fig 4a, but from a silvered preparation in which the parasites are more obvious although the details of their structure are obscured (Robb-Smith [1937] *method for reticulin*, ×650)

for darkfield investigations in addition to the confirmatory blood tests In any case, to neglect nowadays such a clear indication for the *Treponema pallidum* immobilisation test is a major oversight

It was interesting that the conduct of the pathological investigations should have disclosed two extremes in modern laboratory practice In one laboratory the actual interpretation of darkfield examinations was delegated to a technician, in the other laboratory the pathologists personally undertook every step in the performance of the Wassermann reaction and not merely the interpretation of the results Paradoxically, in the laboratory in which there was this insistence on the pathologists' personal responsibility for carrying out the Wassermann procedure it was not regularly the practice to put up parallel confirmatory tests unless the Kahn test was specifically asked for, which was not done in this case

Latent Recurrent Kala-azar

I have not been able to find any previous instance of a recurrence of visceral leishmaniasis so long after what had been considered successful treatment The patient's freedom from symptoms was another exceptional feature of his recurrent infection

The histological pattern shown by the lymph-node biopsy was precisely that seen in cases of acquired toxoplasmic lymphadenitis in adults (Bang 1957, Piringer-Kuchinka et al 1958) Only the presence of the leishmanias distinguished the picture from that of toxoplasmosis, the morphological characteristics of the organisms under the oil-immersion objective were unmistakable In some cases it can be difficult to distinguish confidently in hæmatoxylin-eosin preparations between leishmanias and other particulate bodies, particularly *Histoplasma capsulatum* (Woo and Reimann 1957) Recently, in a personal observation, groups of the small-spore form of *Blastomyces brasiliensis*, separated from their parent yeasts and engulfed by macrophages, were mistaken for *Leishmania brasiliensis* in a biopsy specimen, the lesion was a mucocutaneous granuloma which developed some months after the patient had returned home to this country following a year's stay in Brazil The well-known Flemming bodies (particulate nuclear debris) in lymphoid follicles, which are notoriously liable to be mistaken for histoplasmas, may also be misinterpreted as leishmanias Romanowsky stains are not as helpful in identifying leishmanias in histological preparations as they are in films the periodic-acid/Schiff reaction is often more useful, readily distinguishing fungi like histoplasma from leishmanias (leishmanias may contain particles which give this reaction, but these are minute, and confusion should not result) In all cases in which it is possible—and that should be the vast majority—film preparations should be made whenever the diagnosis of leishmaniasis is considered, for they will readily enable any leishmanias which are present to be correctly recognised

Excision of lymph-nodes for the diagnosis of leishmaniasis was advocated many years ago by Cochran (1912), who, however, recommended this procedure merely so that films could be made from them Cole (1943–44) reviewed 60 cases of kala-azar in the Kapoeta area of East Africa, this is the area where Ethiopia, Kenya, and Uganda meet, and it was probably here that the man whose case is recorded above became infected Cole mentioned that half of his patients showed lymph-node enlargement, usually in the inguinal and femoral groups In one case, indeed, lymphadenopathy was the presenting manifestation, leishmanias were found by lymph-node puncture in 12 out of 27 cases in which this investigation was carried out Kirk and Sati (1939–40) demonstrated the organisms in films of juice obtained by needling apparently normal lymph-nodes in Sudanese cases of kala-azar Cole (1943–44) found urea stibamine to be the most effective drug in his cases Post-kala-azar dermal leishmaniasis developed in 17 of the 38 patients in his series who survived the parasites were demonstrated in scrapings from the skin lesions in 8 out of 12 cases investigated During the period in which he studied the 60 cases of visceral infection he saw only 1 case of oriental sore

In contrast with cases in the Sudan, where Kirk and Sati (1939–40, 1940–41) found that there is often no latent period between visceral involvement and involvement of the skin and lymph-nodes, Napier (1935) found in India that the organisms can scarcely ever be demonstrated in the skin and lymph-nodes during the visceral stage of kala-azar Post-kala-azar dermal leishmaniasis, which was first described by Brahmachari (1922), usually appears a year or two after the visceral disease has subsided, and particularly in cases in which the latter has been inadequately treated it is easily distinguishable clinically from oriental sore, differing from this condition specially in its more widespread involvement of the skin and in the multiplicity of the lesions, which are commonly nodular In view of the lymph-node involvement in the case reported in this paper, and of the patient's earlier history of post-kala-azar dermal leishmaniasis, it is interesting to learn that both leishmanial lymphadenitis and post-kala-azar dermal leishmaniasis are seen more frequently in north-east Africa than in other parts of the world

It is remarkable that the woman's lesion took the form of an oriental sore, typical of infection by *L. tropica*, whereas her husband's disease was of the visceral type associated with infection by *L. donovani*. Shapiro and Btesh (1939–40) mentioned the case of an Arab child in Palestine who simultaneously had kala-azar and cutaneous leishmaniasis of the oriental-sore type: they raised the question whether this boy was doubly infected with *L. donovani* and *L. tropica* or whether *L. donovani* was the cause of both the visceral and the cutaneous disease. It would have been instructive in this woman's case to know whether the transitory inguinal lymph-node enlargement was due to leishmanial infection, as was her husband's lymphadenopathy, or whether it was unspecific.

Transmission of leishmaniasis

There seems to be no doubt that the infection in this case was passed by sexual intercourse. There are very few acceptable reported instances of person-to-person leishmanial infection and none of transmission by contagion.

One foreign author cites Leishman as his authority for stating that the disease can be spread venereally. I have been unable to trace such a statement in any of Leishman's writings, and it seems possible that a comment which he made when writing about the ætiology of kala-azar has been misread: "In the presence of these important gaps in our knowledge of the life-cycle of the parasite any description of the ætiology of the disease must be, in the main, speculative. There appears to be little doubt that the disease is spread by human intercourse, though not by direct 'contagion' in its strict sense" (Leishman 1912). It is clear that sexual intercourse was not implied.

Shortt (1945–46) reviewed the ways in which leishmaniasis might be spread, and he noted that person-to-person transmission was theoretically possible. The organisms may be present in a viable state in nasal secretion and in urine, and they can survive for a day or more in moist soil and for several days in milk. They also appear to be able to withstand desiccation for a few hours. Shortt pointed out that infection can be shown by experiment to follow introduction of the parasite into the mouth or conjunctival sac, thus indicating the possibility of transmission by ingestion or by droplet infection.

Firth (1912) and Berberian (1939–40) reviewed the deliberate, and often traditional, practice of inoculating children and others with oriental sore in order to provide some measure of immunity and to try to ensure that the often unsightly scar of the healed lesion should be in an inconspicuous site. There is no doubt that under these conditions person-to-person infection can occur. Under natural conditions, however, leishmania requires to spend a part of its life-cycle within the body of the phlebotomus vector, undergoing metamorphosis and multiplying before the fly can transmit the infection to a fresh victim. It may be noted that Leishman's (1912) remarks on the ætiology of the disease, quoted above, were written before Mackie's (1915) suggestions about the role of the sandfly as vector, and long before it was finally proved that the infected flies could in fact transmit the disease. Adler (1939–40) successfully transmitted kala-azar to one of five patients with advanced malignant disease whom he inoculated with cultures of *L. donovani*: the incubation period was uncertain but did not exceed five months. Later, Swaminath et al. (1942) transmitted Indian kala-azar to man by the bite of infected sandflies in each of five experiments: the incubation period was between nineteen and thirty weeks or thereabouts. Other experimental studies have confirmed that leishmaniasis can be conveyed in this way, provided that enough time is allowed for the protozoon to complete its cycle of development in the infected phlebotomus before attempting to transmit the infection, and provided that the inoculated volunteers or animals are kept under observation long enough to allow the presence of infection to be recognised. There is no longer any doubt that natural infections with leishmania, including familial and household infections, are ordinarily attributable to the bite of infected sandflies.

Senekji and Beattie (1940–41) studied the development of experimentally produced oriental sores in man. From observations on over 200 cases they found that the incubation period after an intradermal injection of three million leptomonad forms from cultures of *L. tropica* ranged from under two weeks to eight weeks. A single inoculation was sufficient to produce infection in over 99% of their experiments. In the average case a macule appeared at the site of inoculation after three weeks and gradually developed into a slightly scaly, purplish papule with an infiltrated base: in six months the lesion was as large as a "coffee bean." In half the cases ulceration occurred after six to eight months, and the untreated ulcers took nine months to a year to heal. Ulceration was thought to result from incidental traumatisation of the lesion. These observations correspond closely to the patient's account of the development of the vulvar lesion in the case described here. The incubation period in her case cannot be estimated. Manson-Bahr (1954) mentioned that the incubation period of oriental sore is variously stated in days, weeks, or months, periods of three years (Smith 1955) and three and a half years (Fidler 1952) have also been recorded.

Two other methods of transmission deserve mention. Transplacental infection of the fœtus can occur (Hindle 1928, Banerji 1955), Low and Cooke (1926) described a case of congenital leishmaniasis in a child, born in Britain, whose mother had become infected while in India. Blood has also been the vehicle of infection in other circumstances. Chung et al. (1948) recorded the development of kala-azar nine months and ten months after two children had each had an intramuscular injection of 20 ml. of their mother's whole blood as a prophylactic against measles: the mother's infection by leishmania was recognised soon after she had given the blood. Andre et al. (1957) reported a case in France of visceral leishmaniasis in a baby who received at birth an exsanguination transfusion of blood from a donor who had leishmaniasis of the skin and lymph-nodes.

A case of accidental infection with *L. donovani*, in a laboratory worker, has been recorded (Terry et al. 1950). The finger which was infected had been bitten on several occasions by experimentally infected animals.

Other Cases

All the other four cases of leishmanial infection which I have seen during the past five years presented as typical examples of so-called oriental sores. The lesion was solitary in each case.

Two of the patients were children from Cyprus—both were at school in England when the diagnosis was made, but in each case the lesion, which was on the forehead, had already begun to appear when the child left home, six months and eight months earlier. The boys came from different parts of the island, one was Greek and the other Turkish.

In the third case there was also presumptive evidence that the infection was contracted in Cyprus. The patient was a doctor who spent nine months in the island, he had never been elsewhere abroad, and he had travelled to and from Cyprus without stopping en route. His lesion was on the back of one hand and first appeared as a macule about five months after his return to England.

The fourth patient was a young woman who had never been out of England until she went on a bicycle trip to the South of France, where she spent five days camping in the Languedoc not far from Montpellier. She was away from home for altogether fourteen days. Her leishmanial granuloma was on one knee and was first noticed as a little pimple-like lesion five weeks after she left France: ulceration followed within ten days. Autochthonous cases of cutaneous leishmaniasis in southern France have been reported on a number of occasions (Rimbaud et al. 1958).

Diagnosis was made by biopsy in each of these cases and confirmed by examining films of fluid obtained from the lesion Cultivation was not attempted Each patient was given a course of injections of one or another of the quinquevalent antimony preparations which are in current use The lesions healed satisfactorily, except for the usual residual scarring

Summary

A case of cutaneous leishmaniasis occurring in Britain and resulting from marital intercourse is reported

The lesion, on the vulva, was at first mistaken for a primary syphilitic chancre The correct diagnosis was made by biopsy The patient's husband was found to have a symptomless recurrence of visceral leishmaniasis, which he had contracted in north-eastern Africa fourteen years earlier Transmission of leishmanial infection by contagion is extremely rare

Four typical examples of so-called oriental sore were seen in Britain during the past five years In three cases the infection was contracted in Cyprus, and in the fourth case in the South of France

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PREVENTION OF MIGRAINE IN CHILDREN BY PROCHLORPERAZINE

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A DOUBLE-BLIND trial is a satisfactory way of assessing the value of a drug in a condition of such varying severity as migraine In view of the claims made for the value of prochlorperazine ('Stemetil') in the prevention of migraine (Leyton 1957, Schaefer 1959) we have conducted a double blind trial in order to assess its value.

Method and Material

Selection of Cases

All children were seen by us at the Children's Hospital, Sheffield, or the Rotherham and Mexborough Hospitals and county pædiatric clinics All had the classical picture of migraine, with a family history of the same complaint. Children with headaches alone, without the associated symptoms, were excluded Only those who had had frequent attacks over a long period, not less often than about once a month, were included

The double-blind method was adopted The makers of the drug kindly supplied placebo, or control, tablets Having made the diagnosis we prescribed the drug, and the pharmacist, by random sampling, supplied either the active drug or the control When we saw the child again and repeated the prescription, the pharmacist supplied the opposite of that supplied previously Only after we had studied enough patients and tabulated the results based on the parents' opinion did we receive the code which indicated the order in which the active tablet and the control tablet were prescribed

We used a simple scoring method before receiving the code. This consisted of −3 to +3 −3 would mean that the patient was much worse +3 would mean that he was much better +2 meant that he was "better" +1 meant that he was slightly better

32 patients were studied, but some failed to come a second time, so the change-over of drugs could not be effected 28 patients received the active drug, and 29 received the control

The dosage was that recommended by the makers This was 2½ mg twice a day for children 2½ years of age, 5 mg b d. at the age of 5 years, and 7½ mg b d. at the age of 10 years

Results

The 28 patients receiving the active drug scored +39 (see table) The 29 patients receiving the placebo scored +43

SCORES ALLOTTED ON THE ACTIVE AND CONTROL TABLETS

Score	No achieving score	
	Control tablet	Active drug
+3	8	6
+2	8	9
+1	5	4
0	7	8
−1	1	1
−2	0	0
−3	0	0

It will be seen that there was no difference between the two groups The placebo relieved many of the children

There were no toxic effects One mother said that the medicine made her child sick, the offending material was the inert tablet

Summary

In a double-blind trial of prochlorperazine for the prevention of migraine in children, the drug proved no more effective than an inert control tablet The inert tablet relieved many children of their attacks

In the dosage used, prochlorperazine was not of value in the prevention of migraine in children

Our thanks are due to Miss C I Crawford, chief pharmacist, for her help in this experiment, and to Messrs May and Baker for supplying the tablets and control material, and for their advice and help

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" We all know that it is usually possible to single one out of a vast array of possibilities by asking 'Yes or no?' only twenty times A chromosome is able, so to speak, to answer such a yes-or-no question some two hundred million times, which corresponds to the *total information stored in about one thousand large textbooks* "— WARREN WEAVER *in* the Rockefeller Foundation annual report, 1958, p 87

SUBARACHNOID HÆMORRHAGE IN THE ARMY

1950-1956

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In many reported series of subarachnoid hæmorrhage there are factors of selection for which allowance cannot be made Necropsy studies can never be representative, and series from general hospitals often exclude patients who die suddenly or in the first few hours after admission Neurosurgical series are usually biased by exclusion of these early deaths, or by inclusion of patients solely because of recurrent hæmorrhage This study is an attempt to define more accurately certain features of the acute stage of subarachnoid hæmorrhage in young adults, for it is against this background that the results of neurosurgery must be set

Method of Investigation

We have reviewed the records of all Army patients diagnosed during the seven years 1950–56 as having spontaneous intracranial hæmorrhage, intracranial aneurysm, or angioma Hæmorrhage secondary to blood-disease or tumour was not included 10 cases were rejected—5 because of insufficient evidence of subarachnoid hæmorrhage, 2 because there was no recent hæmorrhage, 2 because of inadequate clinical records, and 1 as a case of hypertensive cerebral hæmorrhage in a man over fifty-five years of age 103 cases remained The presence of subarachnoid hæmorrhage was proved by examination of the cerebrospinal fluid in 68 cases, by necropsy in 15, and by both in 20 All but a very few cases were followed for eight weeks from the onset of the illness This period alone—the acute stage—will be considered here.

Classification of Cases

There is good evidence (Walton 1956, and others) that the prognosis in subarachnoid hæmorrhage is closely related to certain features of the early stages of the illness Our cases were assessed according to their state on first admission to hospital, by applying the classification of Smith and Vollum (1956) for tuberculous meningitis

Group 1 includes those who were fully conscious and rational, with no abnormal neurological signs beyond those of meningeal irritation

Group 3 includes all patients who were comatose or completely inaccessible, or who had a complete hemiplegia

Group 2 is intermediate, and includes those with abnormal neurological signs (excluding complete hemiplegia), and those who, despite alteration of consciousness, could still communicate with the examiner

Group 4 comprises all patients who died before admission to hospital These are included to complete the natural history of a condition which is one of the commoner causes of sudden death in young adults

The course of the illness was classified according to a modification of a scheme proposed by Holmes (1957)

TABLE III—RELATION OF CLINICAL GROUP TO COURSE OF ILLNESS

Course	Death				Recovery	Total
	Deterioration		Recurrence		Steady recovery	
	Rapid*	Slow	Fatal	Non-fatal		
Clinical group 1	3 } (5 5%)	2	7	4	32	48
,, ,, 2	1 }	3	1	2	18	25
,, ,, 3	7 (35%)	1	4	1	7	20
Total	11	6	12	7	57	93

* All 10 patients in group 4 showed rapid fatal deterioration.

The course may be one of deterioration, either rapid (with death within forty-eight hours) or slow (with death within fourteen days), without evidence of further hæmorrhage, or initial improvement may be followed by recurrent bleeding, fatal or non-fatal, or recovery may be steady and uninterrupted

Results

Of the 103 cases, 79 were first admitted to military hospitals (43 overseas, 36 in the United Kingdom) and 24 to civilian hospitals (1 overseas, 23 in the United Kingdom) 84 patients were admitted on the first day of the illness, 8 on the second, 4 on the third, 6 on the fourth to sixth days, and 1 (a case of so-called "pseudotumour syndrome") in the third week

Table I shows the cases grouped according to age, and the average incidence per 1000 at risk per year The incidence rises steadily with age, and is four times as great at ages over forty-five as at under twenty, although the number in the former group is small

Table II shows the distribution of cases by age in each clinical group, and the mortality in the first eight weeks Mortality increases with age, and is significantly greater over the age of thirty (63%) than under (27%) (Here, and later, significance is taken at the 1% level) The proportion of cases in group 4 is higher among the older patients, and the mortality is higher, irrespective of the initial clinical state, compared with the younger age-group

TABLE I—AGE-INCIDENCE

Age (yr)	18–19	20–24	25–29	30–34	35–39	40–44	45–49	50+	Total
No of cases	31	35	7	9	10	5	5	1	103
Average annual incidence per 1000 at risk	0·03	0·04	0·05		0·07		0 12		0 04

TABLE II—MORTALITY BY AGE AND CLINICAL GROUP

Age (yr)	18–19	20–24	25–29	30–34	35–39	40–44	45–49	50+	Total under 30	Total over 30	Total
Clinical group 1	2/16	3 15	0/3	1/4	3 5	0 1	2/3	1/1	} 9 55 (16%)	} 8/18 (44%)	} 17/73 (23%)
,, ,, 2	3 7	1 13	0 1	—	0 2	1/1	0/1	—			
,, ,, 3	4/7	0 4	2/2	2/3	1 1	2/2	1/1	—	6 13	6/7	12 20 (60%)
,, ,, 4	1/1	3 3	1/1	2 2	2 2	1/1	—	—	5 5	5 5	10 10
Total	10 31	7/35	3 7	5 9	6 10	4 5	3 5	1 1	20 73 (27%)	19 30 (63%)	39 103 (38%)

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TABLE IV—RELATION OF RECURRENCE AND DEATH TO LENGTH OF ILLNESS

Week after onset	1					2			3	4	5+
Day after onset	1	2	3	4	5	6–8	9–11	12–14	15–21	22–28	29+
Patients at risk	103	88	82	82	79	78	78	77	73	70	66
No of deaths	15	6	0	3	1	0	1	4	3	4	2
Deaths (% per day)	14 6	6 8	0	3 7	1 2	0	0 4	1 8	0 6	0 8	—
No of recurrences	—	—	—	2	0	1	2	2	5	1	5
Recurrences (% per day)	—	—	—	2 5	0	0 4	0 8	0 9	1 0	0 8	—

Table III shows that the significantly greater death-rate among cases in group 3 (60%, as against 23% in groups 1 and 2 together) is due to many more deaths in the first forty-eight hours of the illness The condition of 35% of cases in group 3 deteriorated rapidly, but this is true of only 5 5% of cases in groups 1 and 2 The recurrence-rate is 38% in group 3, and 20% in groups 1 and 2 combined, a difference which is not significant Recurrent bleeding carries a higher mortality than the first hæmorrhage 12 of 19 recurrences were fatal, as against 27 of 103 first hæmorrhages The mortality of recurrent bleeding is also greater in group 3 (80%) than in groups 1 and 2 combined (57%)

The distribution of deaths and recurrences over the first eight weeks of the illness is shown in table IV Death is common in the first five days, but uncommon thereafter Recurrences after the first few days are at a steady rate

Of 58 patients transferred to other hospitals after first admission, 32 were transferred in the first four weeks—9 by air and 23 by road 1 patient's condition deteriorated during flight, perhaps because of heavy sedation 2 other cases, transferred after the first four weeks, also became worse in transit, in both there was probably mild recurrent bleeding In no other case did transport in the acute stage appear to aggravate the patient's condition, despite the long and often arduous journeys undertaken

47 of the 58 patients transferred to neurological units underwent bilateral carotid angiography 24 angiograms were abnormal Of the 11 remaining patients 2 died and were found at necropsy to have intracranial aneurysms Of the angiographic abnormalities 15 were aneurysms, 6 angiomata, and 3 of uncertain nature Thus carotid angiography showed a probable source of bleeding in only 44% of cases investigated

Discussion

In general our findings agree with those of others The incidence of subarachnoid hæmorrhage is found to increase with age, at least up to sixty (Helpern and Rabson 1950, Walton 1956) Although the Service population, from which our cases are drawn, is highly selected by exclusion of the physically unfit, such selection is unlikely to operate against subarachnoid hæmorrhage (the cause of which is usually latent), except for a few cases with migraine and epilepsy We therefore regard the annual incidence given in table I as approximately that in the population of the United Kingdom

That mortality increases with age (Richardson and Hyland 1941, Walton 1956) can be shown even below the age of thirty (table II) The figure of 27% for the death-rate of our patients under thirty may be compared with figures of 31% (Richardson and Hyland 1941) and 27% (Walton 1956), although neither of these series included cases dead on admission Our figure of 63% mortality for patients over thirty is higher than that given by others, but is based on small numbers

Despite the differences in underlying pathology, clinical grouping derived from that used for tuberculous meningitis can be applied satisfactorily to subarachnoid hæmorrhage, as our findings show The general conclusion to be drawn from tables II and III is that, apart from age, the principal prognostic sign is the severity and duration of the disturbance of consciousness, rather than the presence or absence of focal neurological signs (unless there is complete hemiplegia) Thus, hæmorrhage sufficient to cause deep coma on admission carried a mortality of 35% in the first forty-eight hours whereas lesser hæmorrhages, whatever mental disturbance or neurological signs they produced, were fatal in only 5% in the same period Although the incidence of recurrent hæmorrhage is the same in all cases if they survive forty-eight hours, the mortality-rate of recurrences is higher in those who have had severe initial hæmorrhage

Magee (1943) showed that the peak incidence of recurrence is in the second to fourth week of illness Others have confirmed this (see particularly McKissock and Walsh 1956) In our cases there were only 3 recurrences and 2 deaths between the fifth and eleventh days inclusive, and the highest incidence of fatal recurrence was between the twelfth and fourteenth days If surgery is to prevent these recurrences, clearly it must be undertaken before the end of the second week Although angiography is probably more hazardous (Falconer 1954) and less likely to disclose underlying aneurysms (Magladery 1955) if performed in the first few days of the illness than later, the need for information on which to plan surgery seems to justify its being undertaken early (McKissock and Walsh 1956)

A further group of patients for whom surgery may have something to offer is those whose condition deteriorates slowly (Holmes 1957) In Holmes' series (of 100 cases in all) 23 of 43 patients died in this way, but in our series only 6 of 29 The reason for this difference is not clear, but possibly in Holmes' older patients more deaths were due to the sequelæ of prolonged unconsciousness (such as bronchopneumonia) and to the metabolic effects of brain damage

Even in the most favourable situation—that of a mild hæmorrhage in a fit young man—the mortality is 16% in the first eight weeks Of these deaths half should be preventable as they are due to recurrence or to slow deterioration The angiographic demonstration of lesions in less than 50% of cases is disappointing, but recent advances in technique may make a higher rate possible

If early surgery is to be contemplated, early transfer to a specialist centre is imperative Henson (1957) thinks that after the first three or four days there is no undue risk in transporting these patients Our findings do not contradict this view In particular, transport by air, involving two road journeys of up to 50 miles, does not appear hazardous The use of helicopters will make transport by air easier and quicker, and we suggest that this method will be safer for anything more than a short road journey

Summary

The natural history of 103 cases of spontaneous subarachnoid hæmorrhage in Army patients in the years 1950–56 is described

The incidence and mortality rose steadily with age Death was commoner in the first five days than later Recurrent bleeding occurred at a steady rate after the

first few days Recurrences carried a higher mortality than the first hæmorrhage

When the cases were classified clinically in terms of the severity of the initial hæmorrhage, the death-rate was found to be significantly greater among those who were comatose or completely inaccessible, or who had a complete hemiplegia The severity and duration of the disturbance of consciousness was the most reliable prognostic sign

To prevent recurrences, surgery, and therefore angiography, should be undertaken before the end of the second week Unfortunately angiograms showed the probable source of bleeding in less than half of those so investigated Transporting the patients in the acute stage did not aggravate their condition

We should like to thank Dr Honor Smith, Mr W S Lewin, Dr C W M Whitty, and Dr R. G Willison for advice and criticism and the statistical division of the Army Medical Directorate for their invaluable help with the case-records

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SURVIVAL IN AN AFIBRINOGENÆMIC SUBJECT OF FIBRINOGEN PREPARED FROM "TIME-EXPIRED" BLOOD

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THE rising clinical demand for the fibrinogen-containing fraction of human plasma would be difficult to meet entirely with material prepared from freshly drawn blood On the other hand, relatively large quantities are recoverable from the plasma of stored blood, rejected for transfusion when the expiry date of the red cells has been passed The physical properties of the fibrinogen fraction from such blood differ slightly from those of freshly collected blood, and we have therefore observed the survival of the former fraction in the circulation of a young woman with afibrinogenæmia

Material and Methods

The Patient

In this case, previously described in detail (Pinniger and Prunty 1946, Hardisty and Pinniger 1956) the hæmostatic mechanism is normal except that the plasma forms no clot whatever, although a small, flocculent precipitate (corresponding on different occasions to 30–100 mg protein per 100 ml.) has repeatedly been observed to form after incubating recalcified citrated or oxalated plasma for an hour or more In one test the nitrogen content of this precipitate indicated that less than one third of its weight was attributable to protein The patient's platelet count runs at about 600,000 per c.mm blood (normal 150,000–350,000 per c mm blood)

Preparation of Fibrinogen from Plasma of "Time-expired" Blood

The method of Kekwick, Mackay, and Record (Kekwick and Mackay 1954) was adapted for plasma from "time-expired" blood (i e , 21 days or more old) intended also for γ-globulin fractionation The fibrinogen fraction settles less readily from old plasma by the original method, and contains a high proportion of insoluble matter

For the preparation, all reagents and vessels are sterilised. A pool of 60 litres of sterile plasma is prepared from 30–40 "ten-donor" pools selected visually for low fat content, diluted with an equal volume of water and cooled to 0°C. To it are slowly added 13 2 litres of diethyl ether, keeping the temperature between 0°C and −1°C and stirring until the ether has completely dissolved. The mixture stands overnight at 0°C On the following day the clear supernatant is removed and the sludge containing the precipitated fibrinogen is centrifuged at 0°C The precipitate obtained is suspended in 12 litres of a solution containing 80 ml per litre of ether dissolved in 0 15M sodium-chloride, 0 0125M trisodium-citrate solution, centrifuged again, and the supernatant discarded The precipitate is re-dissolved in 6 litres of 0 3M sodium-chloride, 0 0125M trisodium-citrate solution. Warming in a water bath at 37°C accelerates dissolving Fine particulate matter is removed by filtration in three stages through (1) 'Hyflo-Supercel' 300 ml loose powder per litre solution on a Ford CCNA pad (cellulose 70 sq cm. per litre solution), (2) Ford FCB pad (asbestos and cellulose 70 sq cm per litre solution), (3) Carlson EK pad (asbestos and cellulose 140 sq cm per litre solution)

The final solution is bottled, spun-frozen without delay, and dried This fibrinogen solution contains between 1 5 and 2 g protein per 100 ml , of which 60–70% is clottable The diagram obtained by moving-boundary electrophoresis very closely resembles that of the fibrinogen fraction from fresh plasma, suggesting that the lower clottability of this preparation is not attributable to any gross change in the molecular structure or to the inclusion of proteins of other mobilities in the fraction.

After incubation at 37°C for 16–24 hours, a sterile solution 0 2 g per 100 ml. in citrate saline does not clot on addition of thrombin, indicating the presence of plasmin Fibrinogen prepared from fresh undiluted plasma by the method of Kekwick, Mackay, and Record remains clottable for as long as 3 weeks under similar conditions When diluted with an equal volume of water, however, both old and fresh plasma have a short fibrinogen "life" on incubation The dilution of old plasma is necessary to induce more complete sedimentation of the fibrinogen precipitate. It will be pointed out below that this apparent disadvantage of the "time-expired" material does not impair its clinical usefulness

For clinical use the product is freeze-dried in 3–4 g quantities in blood-transfusion bottles and the contents are retrospectively estimated from the nitrogen value of a representative clot. The statements given below of the quantities administered clinically are derived from these determinations

Administration of Fibrinogen Solution

The patient received two intravenous infusions, separated by an interval of 11 months

At the first (batches 105, 107, 110) she was given 13 8 g dissolved in 450 ml. water immediately before a dental extraction Postoperative hæmostasis was achieved within a few hours, as in a normal person, by contrast with the oozing of some days' duration which previously followed tooth extractions in this patient when blood or a blood derivative had not been given

At the second infusion (batches 114, 115), the patient received 17 6 g in 460 ml water a week before the expected date of a menstrual period, because over the previous four months, immediately following her marriage, menorrhagia had been troublesome. The subsequent period occurred a few days later than expected and was very light The plasma-fibrinogen concentration lay between 0 04 and 0 06 g per 100 ml during the menstrual period. Subsequent menstrual periods have not been unduly heavy

Estimation of Fibrinogen Concentration in Plasma

After the first infusion, plasma samples were estimated by one or more of three methods

1 Oxalated plasma was recalcified and allowed to form a clot which was removed after 1–18 hours, and fibrin was determined as N by the *micro-Kjeldahl technique*

2 Citrated plasma was recalcified and allowed to form a clot which was removed after 10–15 minutes and the fibrin determined gravimetrically (Ingram 1952) The appearances of the clot obtained in this method were those of purified fibrinogen rather than of normal plasma Experiments in vitro confirmed that, when time-expired fibrinogen was added to the patient's plasma, fibrin could be recovered as fully as from saline solution

3 Serial dilutions of citrated plasma were incubated with coagulase-positive *Staphylococcus aureus* and the highest dilution in which clumping occurred was noted (Duthie 1954) The method was calibrated by parallel determinations on a plasma whose fibrinogen concentration had been measured by method 2

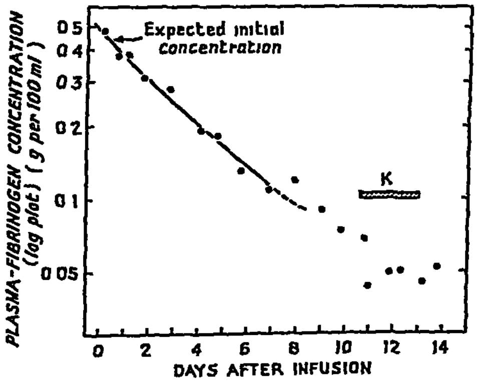
After the second infusion all samples were estimated by method 2

Results

Since, in this patient, previous transfusions had seriously disorganised the superficial arm veins, only rather small samples of blood could be obtained, and some were lost through clotting in the syringe For the same reason, it was not thought practicable to estimate her blood-volume directly, so a tentative figure for the plasma-volume was derived from the body-weight and the venous hæmatocrit

First infusion —By the three methods of determination, five samples over 12 days yielded ten estimates There was no evidence of systematic differences between the methods of estimation, and fibrinogen concentration appeared to regress exponentially against time The pooled results from the three methods yielded a rate (with standard error) for the disappearance of the fibrinogen from the patient's circulating plasma of 14 3 (±1 9) % per day From the regression curve, the fibrinogen concentration at time $t=0$ was 0 31 (±0 01) g per 100 ml plasma, which was only some 57% of the expected concentration which had been calculated from the supposed plasma-volume, but was very near the observed plasma concentration—0 28 g per 100 ml —15 minutes after the end of the infusion This was regarded as a preliminary experiment, mainly confirming the comparability of the three methods of estimation

Second infusion —Eighteen samples were obtained over 14 days and estimated by method 2 (see figure) A regression empirically fitted to the results in the form $y=\alpha+\beta\rho^{t}$ (where y is the fibrinogen concentration at time t, α the asymptote, $(\alpha+\beta)$ the fibrinogen concentration at zero time, taken as 10 minutes after the start of the infusion, ρ the proportion of the fibrinogen remaining in the plasma after unit time, and t the time in days) indicated a plasma concentration 2 hours after the start of the infusion of 0 47 (±0 01) g per 100 ml This agrees well with the observed value of 0 48 g per 100 ml at that time and with the expected concentration of 0 43 g per 100 ml, again calculated from the supposed plasma-volume



Plasma-fibrinogen concentration following infusion of fibrinogen in afibrinogenæmic subject (*second infusion*)

The fitted regression has been drawn in as far as the point where experimental error introduces considerable uncertainty Random scatter is exaggerated at low values by the log plot, but the departure from linearity when log fibrinogen concentration is plotted against time is significant The line below the letter K indicates the duration of a menstrual period Menstruation does not appear to have affected the rate of disappearance of fibrinogen from the circulation

Discussion

Two explanations are possible for the curvilinear relation between log fibrinogen concentration and time, seen in the figure Either the curve might be logarithmic but fall towards the asymptote of a low concentration always present, as in the fitted equation, or it might be the resultant of a superimposed series of movements of fibrinogen between the plasma and various extracirculatory " pools " These explanations are not of course mutually exclusive, although the first seems unlikely because previous observations have failed to demonstrate fibrinogen in this patient's blood except after infusions, nor can the flocculent precipitate previously referred to have contributed to the " asymptotic " low concentration, because it would have taken longer to appear than the time allowed for harvesting the fibrin in this experiment If the second explanation is accepted, the early, rapidly falling portion of the curve could be attributed to the initial stages of equilibration with extravascular fluid, when movement outwards from the plasma is rapid, and the later portion would principally reflect metabolic removal, at a rate masked in the earlier stages It is the slope of this later portion from which the rate of turnover has generally been derived, although of course a rate calculated directly from this slope might include a component representing back-diffusion from an extravascular pool The rate so derived from the tail of the regression of our second experiment is approximately 15% per day the line so fitted, when extrapolated back to zero time, cuts the ordinate at 0 33 g per 100 ml, which represents some two-thirds of the dose injected The separation of these complex effects requires more work, and the problem is being further studied

Meanwhile two points of interest emerge

First, it is curious that our preliminary experiment did not detect the early phase of rapid removal from the bloodstream, although otherwise our results are very similar to those obtained from a comparable infusion given to an afibrinogenæmic boy by Gitlin and Borges (1953) rapid loss of about half the injected fibrinogen was clearly demonstrated during the first 2 days It is hardly conceivable that 5 9 g (43% of 13 8 g), representing a clearance of 1 9 litres of plasma (9 20 of the assumed plasma-volume) can have been sequestered at the tooth socket in the achievement of hæmostasis (although Fitzgerald and Jackson [1956] obtained the astonishing figure of 63 g of fibrin from a retroplacental clot) It also seems unlikely that our findings could be explained by temporary fibrinogenolytic activity, happening to destroy 43% of what was administered, since one would expect to see evidence of equilibration after a short-lived fibrinogenolysis had passed off

On the other hand, in our second infusion, the initial equilibration seems to have occupied at least 4 days, in as much as after this point the observations can be fitted to a straight line on the log plot Perhaps there is great variability in the duration of the early phase of the curve in such subjects, and possibly in our first infusion this phase was already completed by the time of our first blood sample 15 minutes after the completion of the infusion

ESTIMATES OF RATES OF UTILISATION OF FIBRINOGEN IN MAN

Source	Subject(s)	Technique	Mean rate of disappearance of specific activity or material (% per diem)
Madden and Gould (1952)	Normal	Test subjects fed ^{35}S	12
Volwiler et al (1955)	,,	Donor subjects fed ^{35}S	17
Christensen (1958)	,,	^{131}I-labelled	15
Gitlin and Borges (1953)	Afibrinogenæmic	(1) Normal fibrinogen infused	16
		(2) Ultraviolet-irradiated fibrinogen infused	20
Frick and McQuarrie (1954)	,,	Fraction I infused	24
Present case	,,	Time-expired "fibrinogen infused	(1) 14 (2) *ca* 15

In normal subjects the values were derived from measurements of radioactivity, whereas in the afibrinogenæmic subjects fibrinogen was assayed by chemical or immunological methods or with coagulase. The cited rates are obtained from the slow, late exponential portions of the published curves, after the initial rapid equilibration phase was completed The mean of all the quoted values is about 17% per day, and the mean of the three rates derived from normal subjects is about 15% per day For purposes of numerical comparison with other work in which the conception of $^{1}/_{2}$-survival time has been employed, these mean values may be expressed as $^{1}/_{2}$-survival times of about 3 8 and 4 3 days respectively

The *second point* is the survival of our material in the circulation of this patient. The accompanying table gives a series of values derived, as explained above, from the later, slow portion of the curve, obtained from published studies of the turnover of fibrinogen in normal and afibrinogenæmic subjects, it is apparent that our values are near their mean (17% per day) This suggests that fibrinogen prepared from time-expired blood is not destroyed more rapidly in the body than material prepared from fresh blood and may therefore be accepted as an effective substitute for it. It thus seems reasonable to suppose that the plasmin contaminant of the fibrinogen preparation, demonstrated in vitro, is inactivated by the antiplasmin in the recipient's plasma

In this report we have not employed the conventional terminology of half-survival time, because we feel that the term should be reserved for strictly one-component, first-order changes, such as the decay of radioactivity Processes which are really more complex, but which are found to approximate to an exponential for a given period of observation, cannot logically be considered in terms which imply a steady logarithmic change over an indefinite time We have therefore expressed rates of change as percentages removed from the circulation per day during the periods in which observations were being made.

Summary

A method of preparing fibrinogen from the plasma of "time-expired" blood is described

This fibrinogen was twice transfused into a young woman with afibrinogenæmia On one occasion a tooth was extracted and normal hæmostasis was achieved As has been reported with other preparations, about a third to half of the injected dose was rapidly lost from the circulation, but the remainder disappeared more slowly at about 15% per day

This value, which compares well with those obtained in other ways, probably represents the normal rate of turnover of this protein Fibrinogen prepared from "time-expired" blood thus seems likely to be of similar clinical value to that obtained from fresh blood

Our thanks are due to Dr C A Foster for his help with the infusions and with the venepunctures, to Dr N P L Wildy for performing the coagulase tests, to Dr G Bartsch, of the Medical Research Council's Statistical Research Unit, for the statistical analysis of the second regression, and to Dr W d A Maycock for valuable discussion and criticism

(References at foot of next column)

EXACERBATIONS OF CHRONIC BRONCHITIS

TREATMENT WITH OXYTETRACYCLINE

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EXACERBATIONS of chronic bronchitis are among the most common conditions presenting for treatment in general practice in Britain (Pemberton 1949, Fry 1954, Horder and Horder 1954, Logan and Cushion 1958) Until recently treatment was ineffective, but now, for the patient with severe chronic bronchitis, the value of long-term antibiotics in shortening attacks (May and Oswald 1956, Moyes and Kershaw 1957, Buchanan et al 1958) and in preventing them (Edwards et al 1957, Buchanan et al 1958, Edwards and Fear 1958) is reasonably well established The evidence in favour of treating exacerbations with short courses of antibiotics is less conclusive (Elmes et al 1957)

Chronic bronchitis is gradual in its onset In the early stages the patient usually enjoys good health punctuated by "chesty colds" Later on repeated attacks lead to a permanent loss of respiratory function which may remain moderate or may proceed, with exacerbations, to respiratory failure and death In general practice, patients may come for treatment at any stage of this process, and in the cases where permanent respiratory symptoms are moderate or slight the precise indications for antibiotic treatment are far from clear

The Present Investigation

The investigation reported here was a double-blind controlled trial of antibiotic treatment of exacerbations of chronic bronchitis which were mild or only moderately severe In planning the trial, and during the preliminary pilot studies, it was apparent that in severely ill patients the use of control treatments would be ethically indefensible It was not, however, possible to devise a method of assessing severity which could be uniformly applied by all the doctors participating Accordingly the practitioner was asked to classify his cases, on his own judgment, as

A. Antibiotic necessary
B Intermediate.
C. Antibiotic unnecessary

Patients in group A were treated as the doctor thought

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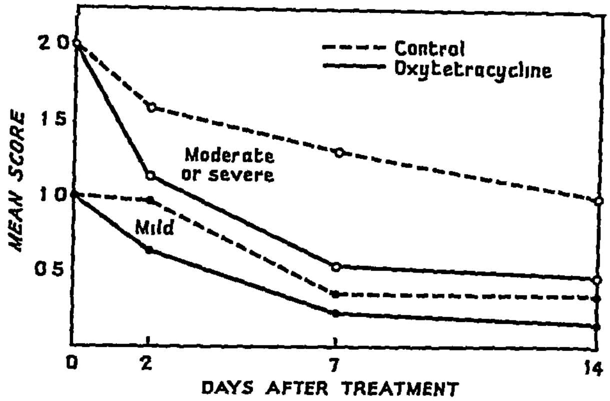
fit, the controlled trial being confined to groups B and C In this way no patient entered the trial if his doctor felt that antibiotic treatment was imperative

The antibiotic selected for trial was oxytetracycline, a drug active against the common pathogens in chronic bronchitis (Flint 1954, Gabrielson et al 1954, Helm et al 1954) and, at least under general-practice conditions, free from serious side-effects Chloramphenicol, while perhaps more effective, is unsuitable for use in a frequently recurring condition, because it may damage bone-marrow A mixture of penicillin and streptomycin gives good results but has to be given intramuscularly and is therefore unsuitable for a blind controlled trial Moreover it carries a small risk of VIII-nerve damage, especially in the elderly

Methods

For the purposes of this investigation chronic bronchitis was defined as "a condition in which there is persistent or recurrent cough with diffuse physical signs in the chest, in which X-ray has excluded other disease " A patient was held to be suffering from an exacerbation when there had been "a sudden worsening (during the past week) characterised by one or more of the following symptoms increased cough, increased volume of sputum, increased purulence of sputum, increased breathlessness or fever " The "baseline" severity of each patient's bronchitis was indicated by his exercise tolerance during the previous summer, according to the following grades



Response of treated and control groups

Grade 2—Able to walk with normal people of own age on level, but unable to keep up on hills or on hurrying because of breathlessness Able to do all housework, but breathless on digging for more than short periods and carrying loads (e g , coal) upstairs

Grade 3—Unable to keep up with fit people walking on the level Able to walk at least one mile flat and to climb a flight of twelve stairs without distress and to perform light household duties

Grade 4—Unable to walk more than 300 yards without pause for breath Able to do sedentary work and the lightest household jobs

Grade 5—Breathless on walking a few yards or on undressing

The severity of the exacerbation was assessed at first presentation, and after 48 hours, 7 days, and 14 days, on a four-point scale, as follows 0, patient's baseline, 1, mild attack, 2, moderate attack, 3, severe attack More objective criteria of severity proved impracticable In some cases intermediate scores (0 5, 1 5, &c) were employed

In addition to recording the severity of the patient's bronchitis, and of the exacerbation, a record was also made of the patient's age and sex and of the presence or absence of the following features of the exacerbation increased cough, increased sputum, increased purulence of sputum, increased dyspnœa, and fever Sputum was sent for culture after the first consultation and after the completion of treatment—all bacteriology being carried out at the same laboratory

TABLE I—CHARACTERISTICS OF THE TREATED AND CONTROL GROUPS

—	Oxytetracycline	Control
Total cases	26	27
Classification at presentation		
B	15	16
C	11	11
Age		
Less than 45	4	7
45–54	6	3
55–64	5	7
65–74	10	7
75 and over	1	3
Sex		
Male	15	16
Female	10	11
Not recorded	1	0
Symptoms		
More cough	26	24
More sputum	21	23
More purulence	16	16
More dyspnœa	23	22
Fever	6	6
Category previous summer		
Grade 2	17	15
„ 3	6	8
„ 4–5	3	3
Not known	0	1
Organisms present in sputum at onset		
Pneumococcus	6	6
Influenza bacillus	6	6
Streptococcus	2	7
Other	2	1
Nil	10	7

As explained above, a patient presenting with an exacerbation of bronchitis was initially assigned by the doctor to one of three categories (A) antibiotic necessary, (B) intermediate, or (C) antibiotic unnecessary Patients in category A were not included in the trial but record cards were completed for them Patients in category B and C were provided with a course of capsules, containing either oxytetracycline (given in the dosage 250 mg q i d for 5 days) or lactose The practitioners each had a series of numbered bottles containing either oxytetracycline or lactose, arranged in random order, the key to the numbers being in the possession of another member of the group All the patients were given oral vitamin B and expectorants, antispasmodics, and other treatment as indicated

Results

Fifty-eight patients were placed in categories B and C and entered the trial The records of two of these patients were inadequate, and in three other cases treatment was discontinued because of possible toxic effects from the tablets (two were on oxytetracycline and one on control tablets) In addition, records were kept of eleven cases in category A

TABLE II—PROGRESS OF TREATED AND CONTROL PATIENTS CLASSIFIED ACCORDING TO THE SEVERITY OF THE EXACERBATIONS

—	Total	Failures	Mean severity score on day			
			1	2	7	14
Mild attack						
Oxytetracycline	11	0	1·00	0 64	0 23	0 14
Control	13	1	0 96	0·96	0 32	0 31
Significance			N.S	N.S	N.S	N.S
Moderate severe attack						
Oxytetracycline	15	0	2 03	1 13	0 53	0 47
Control	14	4	2 01	1 57	1 36	1·07
Significance			N.S.	5%	5%	S

N.S, not significant

Table I shows that the treated and control groups were very similar in composition. For the purpose of analysis the patients were further divided according to the severity at onset, cases scoring 1 being regarded as mild and those over 1 as moderate-to-severe. At assessments after the first, the withdrawal of the patient from the trial because of poor progress was recorded as a failure and scored 4 points.

The response of the treated and control groups is recorded in table II and in the figure. In both the mild and the moderate-to-severe groups the treated patients did better than the controls. In the mild cases this difference was not significant, but in the moderate-to-severe group it was significant at 2 and 7 days.* By 2 days fourteen treated patients were improving compared with only seven control patients, one control had been withdrawn from the trial and put on other treatment. After 1 week, seven treated patients had returned to their base-line condition whereas only 1 control had done so and two further control cases had been withdrawn. By 14 days the advantage of the treated patients ceased to be significant, but a fourth control patient had required alternative treatment.

TABLE III—CHARACTERISTICS OF PATIENTS IN CATEGORIES A, B, AND C

—	A	B	C
Total number	11	31	22
Age			
Under 45	1	6	5
45–54	2	3	6
55–64	2	7	5
65–74	3	12	5
Over 75	2	3	1
Not known	1	0	0
Category last summer			
Grade 2	4	15	17
„ 3	3	11	3
„ 4–5	4	4	2
Not known	0	1	
Symptoms of exacerbation			
Fever	8	9	3
More purulence	11	20	12
Severity of exacerbation at onset			
1	3	8	16
2	3	22	5
3	5	1	1

Further analysis shows that the advantage of the treated over the control patients was largely confined to the patients in category B (intermediate). In fact there is a close correlation between the initial assessment of severity and the classification into categories B and C. The advantage of treated patients over controls applied irrespective of whether any organism was cultured or not.

The eleven patients in group A, who remained outside the trial, were treated with various antibiotics. Two of them died.

Discussion

Our results show that, even where antibiotic treatment is not considered essential, a patient with an exacerbation of bronchitis may derive measurable benefit from it—at any rate if the attack is more than mild.

The criteria on which patients were assigned to category A, B, or C, and on which they were graded for severity, are likely to have varied between participating doctors. Table III compares the features of the patients in groups A, B, and C, and suggests that the decision to give antibiotics was based on the patient's greater age, on the severity of the bronchitis and of the exacerbation, and on the presence of fever and purulent sputum.

Summary

A double-blind controlled trial of oxytetracycline in mild or moderately severe exacerbations of chronic bronchitis is described.

The trial was carried out by a group of general practitioners on a total of fifty-eight patients.

Treated patients recovered sooner and deteriorated less often than the controls. This advantage is statistically significant for patients with moderately severe attacks but not for those with mild attacks.

We are grateful to Messrs. Pfizer for a supply of oxytetracycline ('Terramycin') and dummy capsules, and for the advice of Dr. W. Williams. We are also indebted to Dr. C. M. Fletcher and Dr. N. C. Oswald for their helpful advice.

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PROLONGED TREATMENT WITH STEROIDS IN SEVERE CHRONIC ASTHMA

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CORTISONE and corticotrophin are known to be valuable in the treatment of status asthmaticus, but opinions differ as to their use in chronic asthma. Good results have been reported with prolonged treatment (Lowell et al. 1953, Savidge and Brocklebank 1954a, Davies and Williams 1955, Morrow Brown 1958). In contrast, the Medical Research Council (1956) found that the initial improvement in patients having cortisone, as compared with control patients, was not maintained. At the end of 6 months there was no significant difference between their two groups. Our findings are at such variance with those of the Medical Research Council that we wish to present the results of our own experience, for we consider these drugs to be of real value in severe chronic asthma.

The Trial

A group of fifty patients were treated with steroids for periods of 3 months to 5½ years (mean duration 2·7 years). There were thirty-three women and seventeen men, aged 23–66 (mean 47·2 years). All had severe chronic asthma, resistant to conventional treatments and responding initially to steroids. Most had been unable to work or do their household duties for many months, and frequent hospital admissions had been necessary. The mean duration of asthma was 10·3 years.

Cortisone was given by mouth to thirty patients, most of whom needed 50–75 mg daily Corticotrophin proved more effective in four cases, and sixteen of the later cases were treated with prednisone Response to treatment was assessed by the frequency of paroxysmal dyspnœa, the capacity for exercise and work, and the degree of bronchospasm

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* Significance is calculated by the method of Armitage (1955) from the actual score distributions. This takes into account the non-metrical nature of the scores.

Results

Good results were obtained in thirty-nine of the fifty patients, and there was moderate improvement in five others The results were poor in two women and one man with infective asthma associated with persistent purulent sputum, and three patients died during treatment Twenty-one patients, previously unable to work, resumed their paid jobs or household duties

Illustrative Case-reports

CASE 1 —A woman, aged 33, had had severe asthma for 14 years and had been admitted to hospital twelve times during this period Severe bronchospasm persisted for half the year She felt that her family was neglected She improved within 2 days of starting treatment with cortisone, and for the past $5^1/_2$ years, while taking 25–37 5 mg daily, she has remained almost free of asthma She had a severe relapse 4 weeks after cortisone was stopped in a double-blind trial

CASE 2 —A man, aged 64, had been subject to winter bronchitis with purulent sputum for 30 years During the past 6 years increasingly severe paroxysmal dyspnœa had developed He had been in hospital with asthma three times in the past year, and he was afraid to work Cortisone was started in November, 1956 His condition improved rapidly, and he has since had only moderate bronchospasm for a few weeks each winter in association with infection He has taken cortisone 25–50 mg daily He relapsed 2 weeks after cortisone was stopped in a double-blind trial

CASE 3 —A woman, aged 60, who had had asthma for 21 years, had been forced to give up her light assembly work 6 years previously She had been in hospital continuously for 2 years, having frequent injections of adrenaline and aminophylline In the past $4^1/_2$ years, while taking cortisone 50–75 mg daily, she has had only mild attacks of asthma, and she can now do all her own housework She relapses when given control tablets

Side-effects

Rapid weight gain, due both to improved appetite and to fluid retention, made it necessary to restrict many patients to a low-salt reducing diet Cortisone had to be stopped in two patients because of severe depression Hirsuties and a moon-face developed in three patients

Deaths

Three patients died during treatment

CASE 4 —A woman with asthma, aged 54, was treated for $3^1/_2$ years with cortisone or corticotrophin, and she showed moderate improvement While in hospital with a relapse of asthma associated with bronchitis, she died of cerebral hæmorrhage At no time was her blood-pressure raised The suprarenal glands were macroscopically normal at necropsy

CASE 5 —A woman, aged 41, had asthma which was treated with cortisone 75 mg daily, with good result She was then admitted to hospital with bronchitis, and cortisone was stopped 7 days later severe asthma developed Cortisone 100 mg daily was restarted on the 11th day, but she did not respond, and she died in status asthmaticus on the 19th day Necropsy showed macroscopically normal suprarenal glands

CASE 6 —A man, aged 34, had severe congenital kyphoscoliosis with advanced emphysema and persistent bronchospasm. He had been unable to work for 3 years In 1955 he was in hospital with severe congestive cardiac failure, and he responded very slowly to treatment After discharge he remained cyanosed and dyspnœic on slight exertion, being able to walk slowly only about 200 yards Treatment with prednisone was started in September, 1956 Within 2 days there was much improvement and the bronchospasm disappeared The patient was able to resume clerical work and to dig his garden After 4 months' treatment with cortisone he died at home of acute bronchitis Necropsy was not performed

Death in case 4 was unlikely to be related to treatment, although the cause of her cerebral hæmorrhage was obscure In case 5 it was most unfortunate that cortisone was stopped on admission and restarted in inadequate dosage The third patient (case 6) was an ill man before treatment, and his terminal bronchitis cannot reasonably be ascribed to prednisone

Control Periods

In fourteen cases which were satisfactorily controlled on cortisone, inert tablets were substituted without the patients' knowledge Of these, eight showed a definite relapse within a period of 2 months, two being admitted to hospital in status asthmaticus The condition of five other patients deteriorated more gradually and one remained unchanged Shortly after stopping treatment twelve other patients relapsed These results encouraged us to undertake a double-blind trial, for it seemed important to provide more objective evidence of prolonged benefit from cortisone, even at the expense of distressing relapses

Double-blind Trial

Eleven patients took part in the double-blind trial A twelfth patient moved away from the district during the trial period All were severe chronic asthmatics, who appeared to require a maintenance dose of cortisone There were eight women and three men, with a mean age of 54 years They were seen at 2–4-week intervals, when their symptoms and working capacity were noted The degree of audible bronchospasm was assessed and the 1-second forced expiratory volume ($F E V_1$) was recorded (Thomson and Hugh-Jones 1958)

During an initial observation period of 3–5 months (mean 18 6 weeks), the patients continued to have cortisone in the smallest dose which controlled their symptoms This varied from 25 to 75 mg daily During the next 3 months half continued with cortisone, and the others took identical inert tablets The change from cortisone to control tablets was gradual in order to avoid sudden withdrawal

The standard 25 mg cortisone tablets were replaced by tablets containing 17 mg cortisone for the first control week, and 8 mg for the second control week Inert tablets were continued thereafter Neither patient nor doctor knew whether cortisone or inert tablets were being dispensed.

If a patient relapsed, known cortisone was restarted and continued until the end of the 3-month period The general practitioners knew of the trial and were warned to give cortisone if necessary At the end of 3 months the patients changed from cortisone to inert tablets, and vice versa, for a further 3-month period

Results

During the initial observation period there were minor relapses only But during the period on unknown inert tablets, nine patients had moderate or severe recurrences of asthma, which kept them in bed and prevented work Several of these relapses were of alarming severity

CASE 1 —(See above) This patient developed troublesome asthma on the first day of a family holiday after 4 weeks of the control period For a fortnight she was unable to leave the holiday cottage, apart from short drives when she was confined to the car, and she could do no housework. Her husband was most unsympathetic, and the couple were at loggerheads for weeks She improved rapidly when known cortisone was again started by her doctor

Two patients relapsed during the first fortnight, while the dose of cortisone was being reduced Three patients relapsed at the end of the first fortnight, and the other four 3–5 weeks after starting the control period Improvement was usually rapid after cortisone was resumed, though several patients were persistently more wheezy than usual for up to a month One patient relapsed after 5 weeks of the unknown cortisone period and improved 3 days after restarting known cortisone Another patient remained well throughout both parts of the trial

The F E V $_1$ readings were not helpful as a means of comparing the periods on cortisone and control tablets Because patients often relapsed early in the 3-month periods cortisone was usually restarted by the general practitioner, and spirometry was not done at the time of relapse In four patients, however, where comparable measurements were made in the two periods, the mean F E V $_1$ during the cortisone period was 490 ml and during the control period 380 ml It is interesting that the mean F E V $_1$ of the patient who relapsed while taking unknown cortisone was 480 ml, compared with 360 ml during the control period in the other half of the trial

Thus nine patients relapsed while taking unknown inert tablets, and one while taking unknown cortisone The probability that this distribution of relapses was due to chance is 1 in 1000

Discussion

Most of these severely disabled asthmatics showed considerable improvement with prolonged steroid treatment, and other workers have reported similar good results Our double-blind trial shows more objectively that prolonged control of severe asthma is usually achieved with cortisone It can be argued that prolonged treatment with cortisone merely suppresses the normal adrenal output Relapse on withdrawing cortisone would then result from adrenal suppression We tried to avoid such an acute withdrawal effect by gradual reduction of cortisone dosage

There are features of the Medical Research Council trial which we venture to criticise and which may explain why prolonged benefit from cortisone was not demonstrated

To consider first withdrawals from the trial groups, if we assume that most defaulters failed to continue treatment because of failure to benefit, we find that ten left the control group by reason of continuing asthma (five in status asthmaticus and four defaulters), while only four left the cortisone group (two in status asthmaticus and two defaulters) Thus it seems that the control group was gradually shorn of its severe asthmatics as the trial proceeded, and that cortisone was at a disadvantage in a group with more severe and persistent asthma Cortisone was said to be ineffective after the first 8 weeks, but only two patients having cortisone (one in status asthmaticus and one defaulter) left the trial after 8 weeks by reason of asthma, while five (three in status asthmaticus and two defaulters) left the control group after 8 weeks

The control patients had a higher mean " dose " of placebo (3 54 tablets per day) at the 3-month midpoint of the trial than the patients having cortisone (2 86 tablets per day) This larger number of tablets suggests that asthma was more troublesome in the control group The cortisone group did, in fact, show some advantage at the end of the trial in exercise tolerance and working ability, and the clinicians taking part thought that twenty-three of the forty-nine patients improved during the trial whereas only twelve of the forty-seven control patients improved. Four of the five hospitals concerned were still using prolonged cortisone treatment for approximately two-thirds of both the control and the cortisone groups when they submitted their reports 6–22 months after the trial Our trial, of course, is not strictly comparable to the Medical Research Council trial, in that they compared prolonged treatment with cortisone with prolonged treatment with a placebo, whereas we stopped cortisone treatment even in patients who were doing well on it.

It is important that an adequate amount of cortisone be given, for severe asthma returns in many patients if the dose falls below a critical level We encourage patients to increase their dose if necessary, especially if a chest infection develops, provided always that they take the smallest effective amount Short antibiotic courses are arranged for patients liable to recurrent chest infections In time, many patients are able to reduce their dose of cortisone Six patients have now stopped treatment altogether after long courses of cortisone, and seven require only intermittent treatment The need for continued treatment should be reassessed periodically by the cautious use of control tablets, for patients are very liable to become dependent on cortisone

The risks of prolonged treatment with steroids are well known, and a number of deaths have been reported during treatment (Savidge and Brocklebank 1954b), which may have resulted from adrenal atrophy (Stoner and Whiteley 1954) To prevent such deaths cortisone must be withdrawn gradually in patients treated for long periods, and really adequate doses must be given to cover the stress of operations or infections Patients should carry a card with details of their treatment to warn doctors dealing with such emergencies The weight and blood-pressure should be recorded regularly, the urine tested for sugar, and a chest radiograph taken every 6 months

We conclude that prolonged treatment with steroids is justified and valuable in a small carefully selected group of patients who are severely disabled by chronic or frequently recurring asthma

Summary

Fifty patients with severe chronic asthma were treated with cortisone, prednisone, or corticotrophin for a mean period of 2 7 years The results were good in thirty-nine (78%) Apart from two cases of depression, side-effects were slight

In a double-blind trial with eleven patients, nine relapsed during the control period, and one during the cortisone period The probability that this was due to chance is 1 in 1000

We are very grateful to Dr Richard Doll for the design of the double-blind trial, and for assistance in the interpretation of its results, and to Dr Horace Joules for help and advice The control tablets were kindly supplied by Dr H M Walker and Mr J C H Hanson of Glaxo Laboratories, Ltd, and we appreciate the cooperation of Miss K Knight in dispensing them

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SKIN CHANGES IN HYPOCALCÆMIA

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The association of hair and nail anomalies with hypocalcæmia is well known, and the occurrence of cataracts also well recorded (Albright and Reifenstein 1948)

Simpson (1954) has classified the dermatological manifestations of hypocalcæmia due to hypoparathyroidism and steatorrhœa as follows

(1) Abnormalities of nail and hair growth with latent or manifest tetany of acute onset

(2) Skin, nail, and hair changes after prolonged hypocalcæmia

(3) Secondary infection of skin and nail, often with monilia

While the above trophic ectodermal lesions of hypoparathyroidism have been well recorded, only one reported case of exfoliative dermatitis in this disease could be found (Lachmann 1941) until the recent addition of one further case by Harell-Steinberg et al (1957) This second case had generalised exfoliative dermatitis with sparse hair, leucocytosis, eosinophilia, and low serum-proteins with reversal of the albumin-globulin ratio The skin improved with the administration of irradiated ergosterol These two cases are extremely important since the serum-calcium level is not studied routinely in eczematous patients

In the present paper we describe four further cases of hypocalcæmia These differed in ætiology since one patient had permanent hypoparathyroidism following the removal of a non-toxic thyroid adenoma, one had severe but temporary hypoparathyroidism following the removal of a large parathyroid tumour, and two had steatorrhœa—idiopathic in one and probably cœliac in the other These cases, and two further cases to be briefly mentioned, exhibited a dermatosis which could be related in onset and severity to the level of the serum (or plasma) calcium

Methods

Plasma (or serum) calcium was determined by the standard micro method using oxalate precipitation and titration with permanganate

Throughout this paper we use the term vitamin D to mean either vitamin D_2 (calciferol or ergocalciferol), vitamin D_3 (natural vitamin D or cholecalciferol), or dihydrotachysterol (D H T) By 'AT10' we mean the proprietary form of irradiated ergosterol of which 1 ml is stated to be equivalent to 1 25 mg of pure D H T Where we have used pure vitamin-D preparations the compound has been made up in our own pharmacy in peroxide-free arachis oil with antioxidant and given out in gelatin capsules of various sizes Frequent assays have confirmed the stability of our preparations We have preferred throughout to cite vitamin-D dosages on a mg basis since in the treatment of hypocalcæmia dosages of all preparations thus expressed are closely comparable 1 mg of vitamin D_2 and of D_3—40,000 I U D H T and AT10 have little antirachitic activity in the rat assay method so cannot be measured in international units

Case-records

Case 1—A married woman, aged 63, was admitted to University College Hospital on June 4, 1951, having been referred to us by Dr D Ferriman for further investigations as a possible case of hyperparathyroidism She gave a typical history of increasing pain and muscular weakness, and investigations showed high calcium, low phosphorus, high phosphatase, and X-rays pathognomonic of osteitis fibrosa generalisata A parathyroid tumour was found and removed on July 5, 1951, by Mr W R Merrington, and she recovered well from the immediate effects of the operation A week later, however, she developed acute anxiety (without any of the other signs of tetany) which was found to be due to hypocalcæmia, her plasma-calcium being then 5 6 mg per 100 ml These attacks were relieved by intermittent intravenous injections of calcium gluconate, but the calcium remained low in spite of this, although her bone pains and other signs were improving On July 23, 1951, she developed a generalised rash with severe itching and swelling, especially of her face

On examination she had generalised eczema particularly severe on the face, eyelids, trunk, and lower limbs There was swelling of the face with erythema, scaling, and vesiculation together with excoriations on the arms and thighs There was erythema with scaling of the scalp and sparseness of hair

A drug eruption was thought to be the likely diagnosis, but the only medicament which was being used was calcium gluconate by intravenous injection Intradermal skin tests with calcium gluconate were negative The skin improved a week later and then in another fortnight became much worse with generalised œdema, especially of her face, so that she could not open her eyes This rash was at first attributed to the intravenous calcium It continued, however, when the injections were stopped for a short period and it did not heal finally for about two months In retrospect the first temporary improvement (while large intravenous doses of calcium gluconate were being given) and her final spontaneous recovery coincided with rises of plasma-calcium to about 7 and to 8 mg per 100 ml respectively (see fig 1) She was followed up for several years Her serum-calcium remained normal, she had no further rash We now have reason to believe that this patient also had occult idiopathic steatorrhœa as in the patient described by Davies, Dent, and Willcox (1956) Unfortunately the opportunity to confirm this diagnosis on a further admission to hospital has not yet arisen

Case 2—A married woman, now aged 68, was referred to the psychiatric clinic of University College Hospital by her private doctor on account of severe psychological changes Dr E Roderic-Evans, who saw her there, thought that these might have been precipitated by disturbed metabolism and referred her therefore to one of us

When seen here (Feb 27, 1952) she was found to have pronounced symptoms and signs of tetany, a rash on her hands, and hopelessness, anxiety, depression, and fear of being alone

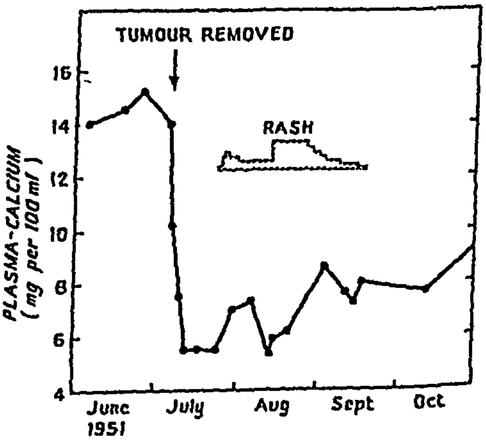

Fig 1—Case 1 relation between plasma-calcium and intensity of eruption

The rise in calcium during July 30 to Aug 6 1951, and on Sept 3, 1951, coincided with heavy intravenous calcium gluconate therapy The final rise in calcium was probably spontaneous

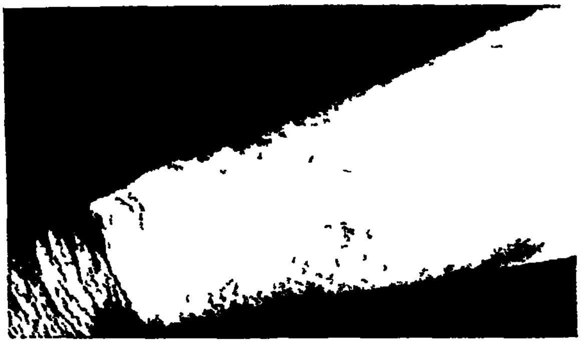

Fig 2—Case 2 eczematous papulo-vesicles on the right arm with redness and scaling

This eruption occurred on the limbs, face, and neck, whenever her serum-calcium level fell below 9 mg per 100 ml

These mental symptoms had recently been so bad that she had begun to consider taking her life.

All these troubles followed removal elsewhere of her thyroid gland in September, 1950, on account of a lump at first thought to be malignant After the operation she was told that it had not been confirmed as malignant and that four glands behind the thyroid had also been removed From then on she has been given thyroid medication. On account of the tetany she was also given at first AT10, but as this did not appear to help, injections of ' Parathormone ' were begun. This relieved her symptoms and she left hospital well in November, 1950, still on parathormone. In January, 1951, she began to have attacks of vomiting, constipation, and weakness, diagnosed at first as " gastric flu " This continued till March, when this was shown to be associated with a serum-calcium of 18 mg per 100 ml and a blood-urea of 116 mg per 100 ml The parathormone was then stopped, and she got better and remained well for about four months All the original symptoms returned, however, in October, 1951 She was then intermittently treated with AT10 and calciferol without much improvement. On Feb 2, 1952, parathormone was again given. It relieved her symptoms for a week, after which it seemed to become ineffective, and she broke down mentally and was soon referred to the psychiatric department at University College Hospital, and thence to us

She then reported that she had a rash between her fingers This had come and gone with each previous worsening and improvement of her signs of tetany, and when severe had spread over her whole hands and forearms On examination, she had gross tetany and was very disturbed mentally, feeling depressed and complaining about everything No other physical signs of disease were discovered Plasma calcium 5 9, phosphorus 6 6, mg per 100 ml Very thorough investigations were then undertaken in the metabolic ward of her response to parathormone and to oral AT10 and calciferol.

We found that she was difficult to control with either form of vitamin D, but we eventually worked out a suitable dosage and later changed her drug satisfactorily to pure D H T We also confirmed the association between the rash (fig 2) and the hypocalcæmia (fig 3) From then until the time of writing (June, 1958) she has been regularly followed as an outpatient She has shown herself to be unusually sensitive to variations in her plasma-calcium Several times during this period she has developed early signs of tetany when her plasma-calcium has fallen slightly (below 9 mg per 100 ml), and at other times she has noted signs of milk intoxication when it has risen to only slightly abnormal levels (above 11 mg per 100 ml) Because of the difficulties in maintaining her plasma-calcium between the narrow limits, we had several opportunities to observe the effects of these changing levels These effects were twofold when the calcium was either high or low she became exceedingly depressed and mentally unstable, when it was low she also developed a rash, which always got better when the calcium was raised to normal or above normal. During this follow-up there were four further occasions (only two are shown in fig 3) on which she had the rash in association with a plasma-calcium of less than 9 mg per 100 ml. She has never had the rash when the plasma-calcium has been above 9 mg per 100 ml. When present for only a short time the hypocalcæmia was associated with only minor itching and eczema between the fingers On two occasions (fig 3) it was more severe and of longer duration and comprised more generalised eczema affecting her lower limbs, face, and neck.

The rash occurring during October and November, 1952, was of particular interest. On this occasion we did not attribute the rash to the slight lowering of her plasma-calcium, for it appeared around her neck and seemed to be related to the dyed fur collar that she was wearing When she stopped wearing the collar, the rash improved a little She had a multicoloured jumper made of wool, which later appeared to produce an eruption on the neck, shoulders, arms, and wrists At this time she was seen in the dermatological department, when patch tests with wool fibres from the incriminated jumper were performed. These patch tests were positive. During this period other garments were suspected of irritating the skin. The rash rapidly improved, however, when her plasma-calcium was raised to normal, so we presumed that the slightly low plasma-calcium (as later in 1956) was the main precipitating cause of this rash. Later, when the plasma-calcium level was restored to normal, the suspected garments could be worn again without causing irritation. Of especial note in this case was the fact that her plasma-calcium has been raised to normal on three occasions with parathormone, once perhaps as the result of a parathyroid graft and on all the other occasions with a form of vitamin D The rash improved equally well whichever treatment was given.

Case 3—A married woman, aged 61, was complaining of an eruption on her hands and arms which had been present on and off for the past eighteen years, though she remembered having occasional skin trouble for the past forty years

When first seen by Dr P J Hare in February, 1957, she had a rash on the hands and forearms which he thought was a contact dermatitis, though there were no apparent contact factors

In July, 1957, she was admitted to St. Pancras Hospital under the care of Dr J F Stokes She was then in cardiac failure, with attacks of paroxysmal supraventricular tachycardia. She was noted to be of short stature and was found to have biochemical and X-ray evidence of osteomalacia We thought that she was probably an adult survivor of cœliac disease. At this time, her skin disease was quite severe Trousseau's sign was positive She had redness, scaling, and slight oozing affecting the whole of her body surface except

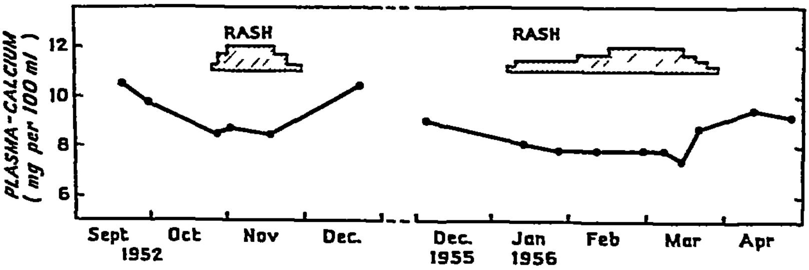

Fig 3—Case 2 relation between plasma-calcium and intensity of eruption

The fall in calcium in 1952 occurred immediately following insertion of a homologous parathyroid tumour into the patient s thigh, other treatment having been stopped We believe it represents the slow and final death of the graft After this the patient received AT10 for some while The prolonged fall in calcium during early 1956 occurred during therapeutic trials of AT10 and pure D.H T in various doses, for which the patient had very kindly volunteered the face, which was relatively spared The nails were thickened and the soles and palms were hyperkeratotic The flexures were moistened by a serous discharge and were particularly severely affected The scalp was very scaly, giving an overall impression of seborrhœic dermatitis in an erythrodermic phase Her hair was thin and brittle

Her hæmoglobin was 64% and the mean red-cell diameter was 7 5 μ This macrocytic anæmia was thought to be an expression of her malabsorption syndrome, and her total fæcal fats were 63% (dry weight) Fat balance showed deficient absorption.

She was treated with digoxin and iron, and was given pure D H T 1 mg b d by mouth A gluten-free diet was not considered practicable Cardiac failure diminished, the plasma-calcium rose, and Trousseau's sign became negative Between December, 1957, and February, 1958, she was maintained fairly well. The plasma-calcium remained low—approximately 8 0 mg per 100 ml —but her skin improved considerably During January D H T was omitted owing to a misunderstanding, and her plasma-calcium fell to 7 2 mg per 100 ml and the skin became much more red, scaly, and itchy The dose of D H T was raised temporarily to 15 mg daily and then lowered to 5 mg daily, and on this dose the plasma-calcium rose from 7 2 to 7 6 mg per 100 ml over the course of four weeks (see fig 4)

She improved so much that she was allowed to go home for Easter in April, 1958. After three days at home during very cold weather, she returned having changed greatly Her rectal temperature was 86°F and she was very sleepy She died in coma on April 9, 1958

Postmortem examination showed the presence of bronchopneumonia, and there were pinpoint yellow areas surrounded by hæmorrhage in both adrenal cortices It was thought that this patient died of hypothermia

Case 4 —A man, aged 63, first attended the dermatological outpatient department in 1953 complaining of a rash which he had had on his legs for the past three months He admitted to some recent loss of weight and had suffered from indigestion The rash was worst on the legs behind the knees and on the sacrum (fig 5) The rash consisted of blue-red erythema with oozing and crusting in the groins, around the genitalia, and on the thighs, buttocks, and sacral area In these areas there was dark bluish-brown pigmentation, with thick scaling and crusting in the folds The eruption was foul-smelling and tacky, and more peripherally there were brown pigmented lichenified areas with bluish-red papules, ill defined, 3–4 mm in diameter The natal cleft was sore The rest of the body was pigmented, pale fawnish-yellow There was fœtor from the mouth, the corners of the mouth were crusted. *Candida albicans* was grown from the mouth and from the groins The nails were grossly thickened, and the tongue was glazed and atrophic

He was admitted to hospital but could not stay in for long and was discharged after a month somewhat improved His rash slowly healed with pigmentation, but relapsed to its former state Grenz rays and local applications helped him to some extent

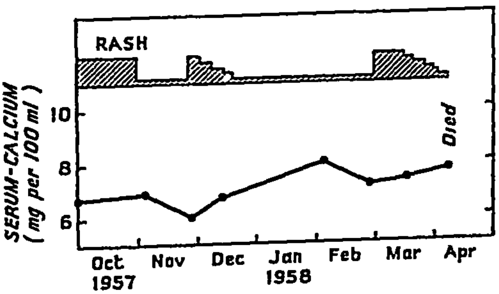

Fig 4—Case 3 relationship between serum-calcium level and intensity of eruption

The patient died before her calcium could be made quite normal and the rash completely healed

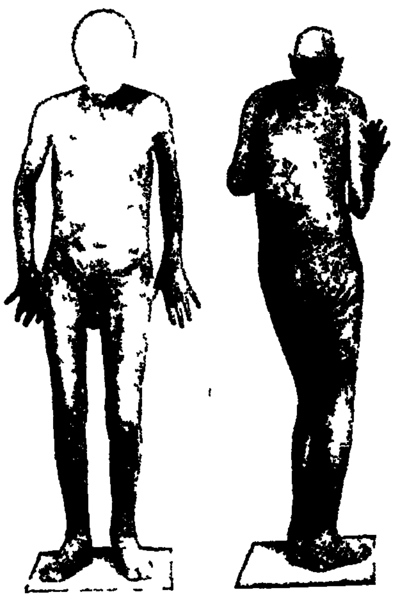

Fig 5—Case 4 redness, scaling, and vesiculation mainly on the trunk and lower limbs

There is pronounced pigmentation of the skin, especially intense in areas affected by the eczematous changes Photograph taken before steatorrhœa was diagnosed, when the serum-calcium was probably in the region of 5 mg per 100 ml

He remained fairly well during 1954, though his skin was always rough and scaly, and in 1955 he was readmitted He was found to have macrocytic anæmia, and was treated with local applications and vitamin B_{12} He was discharged improved

In 1957 he was once more admitted with generalised erythroderma, severe pigmentation, and macrocytic anæmia He was prematurely bald and had clubbed fingers Dr J Nelms (house-physician) suggested that the patient was suffering from steatorrhœa, and the fat-balance and X-ray pictures of barium meal and follow-through confirmed this view He had had chronic bronchitis on and off for ten years, but soon after admission he had an attack of stridor, tingling in the hands, and muscle cramps His serum-calcium level was found to be 5 0 mg per 100 ml and his phosphorus 1 0 mg per 100 ml Trousseau's and Chvostek's signs were positive

He was then seen by one of us (C E D) who agreed that the low serum calcium and phosphorus were due to steatorrhœa Raising his serum-calcium by means of pure calciferol 5 mg b d by mouth improved his chest condition and caused his cramps to disappear and his eczema to heal He was also given 'Diodoquin' (di-iodohydroxyquinoline) orally at first, but it was not considered to have played a part in his improvement and was later stopped

He was discharged well, and remained in fairly good health until his calciferol was stopped in May, 1957, when calciferol ('Sterogyl') 50,000 I U (1 25 mg) b d by mouth was substituted to see if this helped more He rapidly deteriorated, he became weak, and redness and scaling reappeared His serum-calcium level fell to 5 3 mg per 100 ml Treatment by mouth with pure calciferol (5 mg t d s) was reintroduced The serum-calcium level was restored to normal and the skin rapidly improved (fig 6)

He continues to be treated with vitamin B_{12} and oral calciferol (5 mg b d) and remains well

The eczema which became generalised and produced an exfoliative dermatitis in this man was peculiar in that deep pigmentation occurred Skin pigmentation is a common feature in steatorrhœa, and it is thought that it was the presence of steatorrhœa which determined the pigmentation in this patient The pigmentation which he exhibited was, however, more bizarre and deeper than is usually associated with that condition.

Biopsy showed the histological features of eczema with deposits of melanin deep in the dermis as well as in and around the basal-cell layer No evidence of abnormal deposition of iron pigments in the skin could be found

Discussion

We have described here four patients in whom there appeared to be a constant association of a dermatosis with a lowering of their serum (or plasma) calcium levels, the condition always being reversible by raising the calcium to normal. We are not aware that this matter has been reported before in these terms, although it is perhaps not surprising in view of the known associations between hypocalcæmia and other skin lesions. These known associations, mentioned in the introduction of this paper, have occurred when the hypocalcæmia was due to hypoparathyroidism or steatorrhœa. In the cases we describe, these ætiologies are also concerned. That it is the lowered calcium level that is the main cause of the skin lesions seems quite clear, for not only are there several causes of hypocalcæmia, but it seems to be immaterial which particular means was used for raising the calcium to normal. For instance, among these have been the spontaneous return of the patient's parathyroid function, injections of crude parathyroid extract obtained from animals (parathormone), injections of calcium gluconate, and oral treatment with pure calciferol, pure D.H.T., or irradiated ergosterol (AT10). In most instances no other treatment than that mentioned above was given at the time. Local treatment to the skin consisted in bland applications throughout.

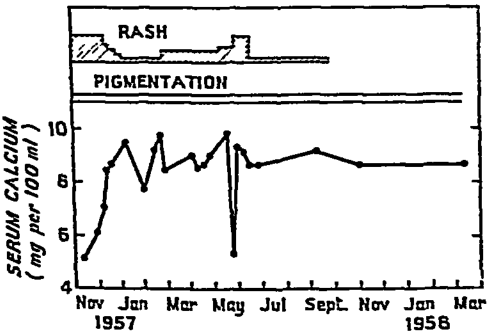

Fig 6—Case 4 relation between serum-calcium level and intensity of eruption

The acute fall in serum-calcium during May, 1957, coincided with a change of treatment to sterogyl, which in the dosage used proved to be ineffective. The serum-calcium level rose again when pure calciferol was reintroduced.

Clearly these skin lesions are an uncommon complication of hypocalcæmia. Apart from these four patients we have so far observed only two further cases in which itching and skin disease developed together with temporary hypocalcæmia. We think these are probably true examples of the phenomenon, but the investigations are inadequate for publication here. There must also be a strong and constant individual factor involved, for the patients mentioned here have always had the rash when we know, or can presume, that their calcium was low. It is clearly important to consider this possible cause of skin disease, especially bearing in mind that the treatment with vitamin D is very adequate and that there seems in such cases to be no alternative treatment.

We wish to stress strongly that classical signs of tetany do not need to be present with marked hypocalcæmia. This is a well-known clinical observation, although published reports do not stress it. Of our cases, case 1 showed this feature conspicuously, for she was repeatedly observed over a period of three months with very low calcium levels, but never manifested positive Trousseau or Chvostek signs, spontaneous cramps, or carpopedal spasms. It was fortunate that in her particular case we were expecting her calcium to fall owing to her having had a large parathyroid tumour removed and having with it very severe bone changes. In two of our other cases it is painfully apparent that we were much slower to make this diagnosis. We can only suggest that if an adult patient with skin disease and no signs of tetany has a scar on the neck or is less than 5 ft. tall, the plasma-calcium should certainly be determined—perhaps sometimes in even less obvious circumstances.

Impetigo herpetiformis was first described by Hebra (1872) and is a pustular dermatosis associated with fever and severe prostration. Four of his five cases died. Some hundred cases are now recorded, and these were reviewed by Hvidberg (1957). The disease is more common in women, though cases are recorded in men. Women very often acquire the disease, or recurrence of it, during or immediately after pregnancy. A striking proportion of women have a history of thyroidectomy. Beek (1951) records typical hypoparathyroidism in twenty-four out of fifty-seven cases. He concludes that some cases are due to endocrine imbalance, while some are caused by an infection. While this severe pustular disease bears no clinical resemblance whatever to the cases of "hypocalcæmic dermatitis" which we have described, the relationship to parathyroid function seems to be more than a coincidence. One of Hvidberg's cases, a woman with typical impetigo herpetiformis in pregnancy, proceeded to have attacks of generalised erythroderma twelve years later.

Many workers have considered the dermatological significance of calcium metabolism. The subject was reviewed by Goldsmith and Hellier (1954), and Wiener (1955) mentions the anti-inflammatory action of calcium therapy in mustard-oil conjunctivitis experimentally induced in rabbits. Calcium-gluconate injections have been used in the treatment of urticaria, pruritus, and eczema with varying results. The value of this mode of treatment may be explained on the basis of the work of Chambers and Zweifach (1947). These workers believe that calcium ions are required to restore the damaged cement substance which serves in the densification of vessel walls.

Calcium metabolism has been studied in many other dermatological conditions. The fact that calciferol itself, or perhaps the mild hypercalcæmia resulting from its administration, can profoundly affect the skin reactivity to disease processes is quite obvious from the common clinical experience of the remarkably beneficial effects of calciferol in lupus vulgaris, though this is rather a special case. Furthermore our case 2 was shown to be sensitive to dyed wool fibres only while she was hypocalcæmic. This situation may clearly be of practical importance in skin testing to external irritants. In this paper we have not, however, attempted to explain the skin changes in cases of hypocalcæmia in terms of disordered skin physiology, since we have nothing to add to this difficult matter.

Summary

In patients with diseases of three different ætiologies, severe skin changes were closely associated with temporary hypocalcæmia.

In each case dramatic improvement occurred, often repeatedly, when the plasma (or serum) calcium became normal or was restored to normal with vitamin D, parathyroid hormone, or calcium-gluconate injections.

These facts are considered to be highly suggestive of a close association between "skin health" and plasma-calcium levels in certain patients.

Since the presence of hypocalcæmia may not be clinically obvious from the presence either of overt tetany or of a known cause of tetany, this possibility should be borne in mind, especially as treatment is so satisfactory

We wish to thank Dr J F Stokes for permission to publish case 3, and Dr P J Hare for case 4 Mr A Bligh kindly took the clinical photographs and Mr V K Asta drew the diagrams

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OVERWEIGHT IN PREGNANCY

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THAT overweight in pregnancy increases the risk to the fœtus has long been known (Smith 1916)

Matthews and der Brucke (1938) studied 200 pregnant women whose weight was over 200 lb 75% of them had some complication of labour They showed a pronounced increase in the incidence of pre-eclamptic toxæmia, malpositions, long labour, maternal distress, and operative delivery These findings were confirmed by Odell and Menger (1945) Tompkins et al (1955) found that patients 20% or more overweight or underweight were especially likely to develop pre-eclamptic toxæmia Williams (1957) found that in cases of pre-eclamptic toxæmia the patients' initial weight as well as weekly gain during pregnancy were on average higher than normal

Hamlin (1952, 1953) found that one of the most important factors in the prevention of eclampsia and pre-eclamptic toxæmia was control of diet and weight gain in pregnancy He reported that by this means he had reduced the incidence of eclampsia from 1 in 500 to 1 in 7000

Another danger of excessive weight gain in pregnancy is that the patient may remain permanently obese (Gurney 1936, Greene 1939, Sheldon 1949, Richardson 1952) In a personal series of 300 obese parous women attending a medical outpatient department, 226 (72%) stated that their obesity dated from pregnancy

Only 45 of these had shown any previous tendency to obesity In all but 30 the obesity had increased with every pregnancy Moreover, there seems little doubt that their maternal obesity seriously impaired their health 50 of them, seen consecutively, were matched for age and sex with 50 medical outpatients who were not obese It was found that in the previous five years the obese group had had three times as many hospital appointments as the non-obese group, chiefly in the departments of gynæcology, surgery, physical medicine, and casualty They had also been admitted to hospital more frequently, chiefly for minor gynæcological procedures There is growing evidence that successful treatment of their obesity has improved the general health of these women and considerably reduced the frequency of their attendances at hospital

Hamlin (1952, 1953) believes that primiparæ should not gain more than 8 lb (3 6 kg) between the 20th and 30th weeks of pregnancy Hughes (1951) stated that a gain of more than 1 lb per week after the fifth month of pregnancy pointed to the need for close observation of the patient A woman whose initial weight for height is more than 25% above any " standard " table is, by general agreement, overweight, and a weight gain of more than 28 lb during pregnancy is generally regarded as excessive All the patients studied here were outside these standards, many of them considerably

Sheldon (1949, 1953) and Richardson (1952) agreed that excessive increase of weight during pregnancy was due to increased appetite and stressed the possible importance of psychogenic factors A patient in the present series stated that she always knew when she was pregnant, even before the first missed period, because she felt unusually hungry Many patients who gain excessive weight in pregnancy feel hungry all the time 100 consecutive patients in the present series were asked about this and 52 admitted to it Others found that the frequent ingestion of carbohydrate was the best way to control nausea A woman who normally controls her appetite for the sake of her figure may regard her inevitable change of shape during pregnancy as a justification for " letting herself go ", she may believe that she must " eat for two ", or fear that, by depriving herself, she is depriving the child Lastly, many women who give up work during pregnancy are bored while waiting for their babies, they find themselves at home all day, surrounded by food, and eating helps to pass the time

Material

This is an account of the management during pregnancy of 25 multiparous patients each of whom had, during one or more previous pregnancies, gained 42 lb or more, and of 10 primiparous patients who, in the first five months of pregnancy, gained a minimum of 20 lb 15 of the patients in the multiparous group were being treated by me for obesity when they became pregnant, and, of these, 7 had reached normal weight The remaining 10 multiparæ were referred from the antenatal clinic because of their histories of excessive weight gain, and, of these, 7 were obese All the primiparous patients were referred from the antenatal clinic on account of excessive weight gain

Methods

These patients were all treated in the obesity clinic, which is part of the medical outpatient department of St James' Hospital As far as possible they were seen immediately after their visits to the antenatal clinic

At the first visit a medical history was taken and the patient was fully examined In addition, information was sought concerning appetite and food habits and the kind of life the patient led, so that her eating habits could be adapted to it Special note was taken of food preferences and of cravings for special articles of food A history of obesity in the patient's family was also recorded

Advice was then given about the diet In all cases a low-carbohydrate diet was recommended Typical advice was " Eat not more than two slices of bread per day and nothing else whatever containing flour, sugar, or potato Eat as much as you like of meat, fish, eggs, vegetables (other than potato), salad and fresh fruit " Patients who were eating large quantities of foods such as rice or nuts were advised to reduce their intake of these It was often necessary to enlarge on details—for example, to emphasise that all biscuits and bread contain flour, and that an article of food may not be eaten just because it is advertised as " non-fattening " or " slimming "

Drugs were only used when it was considered that the patient's weight could not be controlled without them 4 of the multiparous patients had been on dexamphetamine sulphate before they became pregnant, and these were kept on the drug throughout 2 other multiparæ and 1 primipara were started on dexamphetamine sulphate during pregnancy There is no evidence that this drug is contraindicated in pregnancy, and no ill effects were observed.

These patients were all seen by me at intervals of one to four weeks. The interval depended on the degree of difficulty experienced by the patient in controlling her food intake, and on her weight change between visits.

Results

During the pregnancies the 25 multiparæ gained an average of 18 lb (standard deviation 10 lb) compared with an average of 59 lb (standard deviation 16 lb) in previous pregnancies when their weight had been unsupervised and 49 lb (standard deviation 14 lb) in pregnancies where their weight had been supervised in the antenatal clinic. Only 3 of them gained 28 lb or more, and 2 of these had already gained 24 and 26 lb when referred to the obesity clinic at 20 and 19 weeks respectively.

The 3rd had had uncontrollable craving for chocolate since childhood, and this increased during pregnancy. She gained 36 lb during this, her third, pregnancy, which was the largest gain in the group. During her second pregnancy she had gained 49 lb despite attempts in the antenatal clinic to control her weight. During her first pregnancy she had received no instruction regarding her weight and had gained 63 lb.

Among the 10 primiparæ and 10 multiparæ referred from the antenatal clinic on account of excessive weight gain, the average weekly gain fell from 1·8 lb (standard deviation 0·4 lb) to 0·6 lb (standard deviation 0·2 lb) although they attended the obesity clinic in the second half of pregnancy, when weight gain is normally greatest. None of these patients gained more than 14 lb after the 20th week of pregnancy, or more than 9 lb during the 20–30 week period. The 10 multiparous patients had, during their previous pregnancies, gained excessive weight throughout.

All the 35 pregnancies in which the weight gain was controlled in the obesity clinic ended in the normal delivery of a healthy infant. In the previous 43 pregnancies of these women in which the weight gain had not been successfully controlled, there had been 5 stillbirths, 6 forceps deliveries, 3 cæsarean sections, and 8 cases of pre-eclamptic toxæmia necessitating admission to hospital.

Discussion and Conclusion

Experience in treating obesity has shown that advice, however sound, is seldom sufficient for satisfactory weight loss when it is given only once. The patient must be seen at short intervals to reinforce and repeat the advice and to encourage, praise, or admonish. In difficult cases it is often necessary to discuss in detail the patient's eating habits, to vary the diet in accordance with her life circumstances, to suggest recipes and methods of food preparation, and to encourage the patient to try new articles of food; repeated encouragement and advice are especially necessary in such cases because long-standing habits are hard to change, and the attempt often causes the patient much anxiety.

By these methods many obese patients, hitherto regarded as "untreatable", can be helped to regain normal weight. The same principles have been applied successfully to patients with excessive weight gain in pregnancy, not controlled by advice in the antenatal clinic. Since pregnancy is a common starting-point of obesity in later life, the control of excessive weight gain in pregnancy is important, not only for the outcome of the pregnancy, but also for the future health of the patient.

This work was done during the tenure of a Nichols research fellowship of the Royal Society of Medicine.

(References at foot of next column)

TOTAL EXCHANGEABLE POTASSIUM IN INFANTILE MALNUTRITION

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ONE of the characteristics of severe protein malnutrition in infants is a profound electrolyte disturbance (Gomez et al. 1957). Balance experiments (Hansen and Brock 1954) have provided indirect evidence of a depletion of potassium and an accumulation of sodium in the body. These changes are reflected in muscle, as shown by the analysis of biopsy specimens (Frenk et al. 1957, Waterlow and Mendes 1957). Further evidence of potassium depletion has now been obtained by measurement of total exchangeable potassium (Ke).

Since the original observations of Corsa and his associates (1950), many studies on exchangeable potassium have been made in adults, in both health and disease (O'Meara et al. 1957, Edelman et al. 1958, Flear et al. 1958). Studies have also been reported in normal neonates (Christian and Talso 1959), normal infants and children (Corsa et al. 1956), and in children with the nephrotic syndrome (Gribetz et al. 1954). We have, however, been unable to find any record of such measurements in malnourished children.

Method

^{42}K,† as a sterile solution of potassium chloride, was given by intramuscular injection in a dose of 1 µC per kg body-weight.

The amount injected must be accurately known. This was achieved by weighing the bottle containing the solution before and after filling the syringe. The syringe was washed out after the injection, and the radioactivity measured in the washings.

Exchangeable potassium (Ke) was calculated from measurements on the urine.

Blood was not used, because an unjustifiably high dose of isotope would be needed to obtain a measurable level of radioactivity. Moreover, in these severely ill children the number and size of blood samples removed should be kept to a minimum. Wherever possible three separate samples of urine were collected at intervals from 22 to 31 hours after the injection. In all the later measurements the urine was concentrated about five times by evaporation in order to increase the accuracy of the counting. Radioactivity was measured with a well-type scintillation counter, urinary potassium was measured with the flame photometer.

Exchangeable potassium is given by the formula

$$\text{Ke (mEq)} = [(\text{counts injected}) - (\text{counts lost between injection and measurement})] \times \frac{{}^{39}\text{K concentration in urine (mEq per litre)}}{{}^{42}\text{K concentration in urine (counts per litre)}}$$

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† Obtained from Atomic Energy Research Establishment, Harwell, Berkshire.

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TABLE I—PRELIMINARY STUDY OF EXCHANGEABLE POTASSIUM IN 12 CASES OF INFANTILE MALNUTRITION

Patient no	Age (months)	Weight (Kg)	Total Ke, mEq	Ke per Kg body-weight, mEq
Early cases				
1	12	4 90	145	29 6
2	6	5 35	159	29 7
3	5	3 18	91	28 6
4	5	3 35	152	45 4
5	10	5 95	170	28 6
6	10	4 22	72	17 1
7	20	7 40	209	28 3
8	9	5 30	86	16 2
Recovered cases				
9	18	6 84	264	38 6
10	18	6 10	287	57 0
11	7	6 35	203	31 8
12	18	4 10	157	38 3

In most cases a complete collection of urine was made from the time of injection to the time of measurement The urinary loss of isotope was then measured directly and averaged 4 7% of the injected dose in the first 22 hours When for any reason urine collections were incomplete the urinary loss of isotope was estimated as 5% of the dose

No allowance has been made for fæcal loss

In the adult this is normally insignificant compared with the amount lost in the urine (Corsa et al 1950) However, in infants with diarrhœa and coexistent potassium depletion the fæcal loss of potassium may exceed the urinary loss The effect of neglecting fæcal loss will be to increase the apparent value for Ke In adults it has been recommended (Corsa et al 1950) that oral potassium intake should be restricted during the period of measurement We did not think it justifiable to do this in our cases

In the present series, equilibration of injected ^{42}K, as judged by a constant specific activity in the urine, appeared to be virtually complete by 22 hours In adults 95% equilibration occurs between 18 and 40 hours after injection, even in the presence of œdema (Corsa et al 1950, Blainey et al 1954, O'Meara et al 1957)

Material

The cases studied presented the clinical characteristic of severe malnutrition that have been described in previous reports from Jamaica (Waterlow 1948, Jelliffe et al 1954)

Results

A preliminary study was made in twelve cases (table I) The urinary loss was not measured directly, but was assumed to be 5% of the dose The mean Ke in eight malnourished babies soon after admission to hospital was 27 9±3 0 mEq per kg body-weight, and in four recovered cases 38 9±2 8 ‡ mEq

The results in a second series of twenty-two cases are summarised in table II The mean Ke in six babies who had been in hospital for less than a week was 31 6±3 2 mEq per kg In sixteen children who had been in hospital for more than a week the mean Ke was 41 4±1 3 mEq

The results expressed in this way indicate that on the average the malnourished babies had lost about 25% of their exchangeable potassium

In our cases the serum-potassium level gives no indication of the presence of extent of body-potassium depletion This agrees with previous observations, such as those of Moore et al (1954) on adults

Muscle, on the other hand, reflects more closely the changes in Ke In thirteen cases muscle biopsies were done at the time of measurement of exchangeable potassium The muscle potassium content was measured by the method previously described (Waterlow and Mendes 1957), and related to D N A (desoxyribonucleic acid) phosphorus, as the most constant cellular constituent

Fig 1 shows that there was a good deal of variation, but even in this small number of cases a significant correlation was obtained between Ke and the potassium content of muscle Red-cell potassium seems not to vary in the same way as muscle potassium (V G Wills, unpublished data) From the practical standpoint this is unfortunate, since it would be so much easier to measure

TABLE II—EXCHANGEABLE POTASSIUM IN 22 CASES OF INFANTILE MALNUTRITION

Time in hospital	No of cases	Mean Ke per Kg body weight (mEq)
Less than a week	6	31·6±3 2
More than a week	16	41 4±1 3

There is evidence that one effect of cellular potassium depletion is an inability on the part of the kidney to concentrate hydrogen ion after an acidifying dose of ammonium chloride (Clarke et al 1955, Smith 1959) This test was done in twenty-one cases immediately after the measurement of exchangeable potassium Fig 2 shows a close correlation between the extent of potassium depletion and inability to acidify the urine

Discussion

Our observations confirm the original finding of Hansen and Brock (1954) that infants with protein malnutrition are severely depleted of potassium They suggest, moreover, that this depletion affects cell function in at least one organ, the kidney On the other hand the quantitative interpretation of the results is not easy, since no standard of reference is entirely appropriate In well-nourished children with gastroenteritis there is a loss of potassium in excess of the loss of other tissue components (Darrow 1946) But in these malnourished infants it may be argued that the reduction in Ke merely reflects a reduction in tissue mass, and not a *specific* depletion of potassium To some extent this is true measurements of body water (Smith, to be published) have shown that even in the absence of œdema the body of the malnourished baby contains an increased proportion of water, and hence a decreased proportion of solids In the present

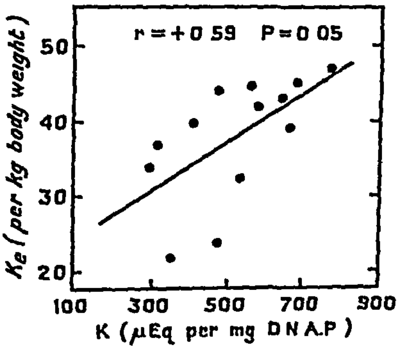

Fig 1—Relationship between exchangeable potassium and muscle-potassium content

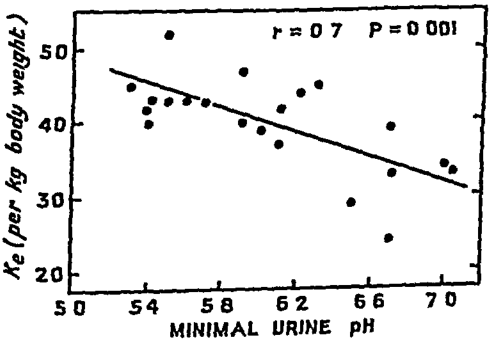

Fig 2—Relationship between exchangeable potassium and minimal urinary pH after a standard load of ammonium chloride

study we have not measured Ke and total body water at the same time in the same case Therefore we are not able to state with certainty whether the depletion of potassium is greater or less than that of the body solids as a whole In one tissue, muscle, there is evidence of a specific or extra loss of potassium, since the ratio of potassium to non-collagen nitrogen is significantly lower than in normal muscle, even after 7–10 days treatment (Waterlow and Mendes 1957) This fits in with Hansen and Brock's (1954) finding that during recovery more potassium was retained than nitrogen (in comparison with the ratio of these two elements in normal tissues), but it cannot be assumed without further investigation that a specific loss of potassium occurs from organs other than muscle

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‡ Standard error of the mean

From the practical point of view, these measurements suggest that the malnourished infant may have lost at least a quarter of its exchangeable potassium, thus an infant of 6 kg might have a deficit of some 60 mEq In this unit we normally give a potassium supplement of about 20 mEq per day (as potassium acetate), in addition to the 15 mEq or so supplied by the diet Even when muscle analysis indicates that the body is depleted of potassium, balance measurements show that retention of ingested potassium is by no means completely efficient Supplementary potassium must therefore be continued for a considerable period—perhaps for 10 days or more Restoration of a normal serum-potassium level must not lead one to assume that the body stores are repleted

Summary

In infants with severe chronic malnutrition the total exchangeable potassium (Ke) was measured by the isotope dilution method Ke per unit body-weight was found to be reduced by 25–30% After recovery normal levels were found

The reduction in Ke was accompanied by a loss of potassium from muscle, and by inability to produce an acid urine in response to a test dose of ammonium chloride

The serum-potassium level is no guide to the extent of depletion of body-potassium

In treatment it is necessary to continue potassium supplements for at least 10 days, since even in the presence of depletion potassium is incompletely retained

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New Inventions

A SPIROMETER FOR MEASURING THE FORCED EXPIRATORY VOLUME WITH A SIMPLE CALIBRATING DEVICE

THE forced expiratory volume (F E V), or amount of air a subject can exhale forcibly in a short time (usually 0 75 sec or 1 sec) after a full inspiration, is now widely used as a measure of ventilatory capacity (for terminology see Gandevia and Hugh-Jones [1]) It can be measured either by a recording spirometer with fast recording kymograph [2] or with a simple spirometer, the rotation of whose wheel shows the volume expired The volume over a fixed time period is recorded by a pointer lightly held at the centre of this wheel and restrained from moving with it during the selected time by a solenoid actuated by an electronic timer [3]

The latter type of apparatus, of which an improved form is described here, has the advantage of providing a reading without the necessity of analysing a paper record, and is thus well suited both for routine use in the clinic where an immediate answer is needed and for field surveys where large numbers must be rapidly examined Up to the present a major disadvantage of this type of instrument has been that it is possible for errors in the electronic timer and relay to go undetected The testing device described here overcomes this difficulty

Spirometer

The spirometer (fig 1) has a 7-litre bell and a breathing tube of $1^3/_8$ in diameter set at an angle of 45° to the canister so that compensation can be made for tables of different heights This tube has a small inspiratory valve in the lower side to prevent

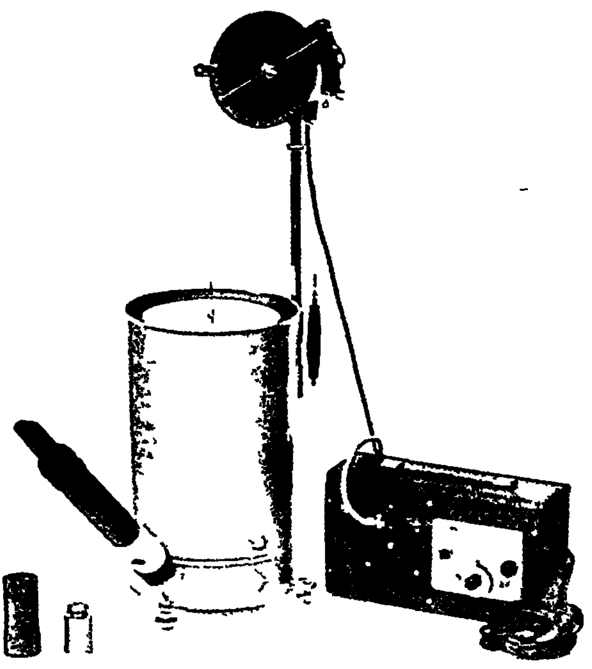

Fig 1—The apparatus with calibrating device

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[1] Gandevia, B , Hugh Jones, P *Thorax*, 1957, 12, 290

[2] Kennedy, M C. S *ibid* 1953 8, 73

[3] Gaensler, E A *Science*, 1951, 114 444

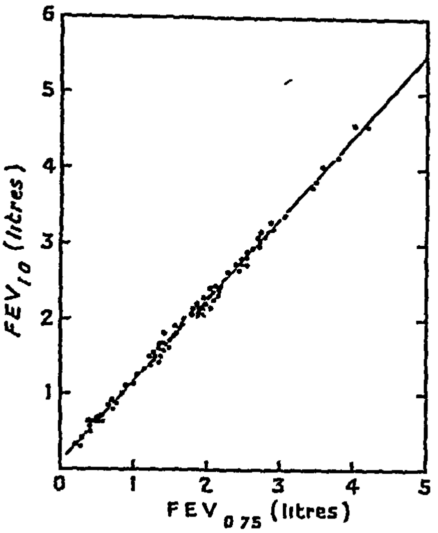

Fig 2—The relationship between F E V$_{0\ 75}$(x) and F E V$_{1\ 0}$(y) in 100 subjects The straight line is the linear regression $y=1\ 08x+0\ 09$

aspiration of water by the subject The black bakelite wheel on the spirometer head has a double white engraved scale, the outer one in litres and 0 05 litre, and the inner one, for recording the indirect M B C, in litres per minute The latter scale (the E F R$_{40}$ of Kennedy) is the F E V$_{0\ 75}$ multiplied by 40, and should therefore only be used when the timer is set for 0 75 sec Both scales are corrected to B T P S, assuming a water temperature of 20°C Their accuracy at this temperature is within ±1 5% A change of ±5°C will cause an error of less than ±2% in the readings, and it is therefore usually unnecessary to correct them further

There are two pointers, the fixed one indicating the vital capacity and the movable one the F E V The back end of the movable pointer engages a catch operated by the solenoid which is only energised during the time period set on the electronic timer The timing cycle, which is adjustable, is initiated through a microswitch on the head immediately 100 ml of air has entered the spirometer This 100 ml volume delay is incorporated to reduce errors in readings due to the subject hesitating at the start of expiration It makes no appreciable difference in normal breaths as the pointer is arranged not to pass the zero until this volume has been expired

The timer, manufactured by Venner Electronics Ltd, is mains operated from an alternating current supply of 200–250 volts and 40–60 cycles per sec It can be set to operate over any time periods from 0 5 to 3 0 seconds

The Calibrating Device

This consists of a 1-in length of 'Tufnol' rod bored to $^1/_2$ in internal diameter and made to attach to the spirometer in place of the breathing tube, and a 500 g weight which is hung on the hook at the bottom of the existing counter-weight The tufnol tube is accurately machined, and damage to its bore will affect the calibration

With the calibrating tube and extra weight in place the spirometer bell is gently depressed until the block on the spirometer wheel makes contact with its stop It is then suddenly released and air is drawn through the orifice into the bell at a flow-rate which is constant for a given spirometer, tube, and weight, the machine will therefore record its own F E V, the values of which, corresponding to time intervals of 0 75 and 1 0 second, are supplied with each apparatus The mean of three readings should agree with the appropriate stated value within ±0 05 litre and the individual readings should not deviate from each other by more than this amount, as the repetitive accuracy of the timer is ±2% If the mean lies outside these limits the cause should be sought and if necessary the timer adjusted

As the air-flow rate at the end of the first 0 75 or 1 0 second of a forced expiration is relatively very low compared with the earlier part, an error in the timer giving a change in the calibration within these limits has been found to affect the recorded F E V less than ±0 6%

Time Interval

The F E V is commonly measured over either 0 75 or 1 0 second and in order to relate these values we studied 100 subjects using a special apparatus with two pointers operated by separate timers The group comprised 20 members of the staff, 60 employees of a light industrial factory for men partially disabled by coalworkers' pneumoconiosis, and 20 inpatients mainly suffering from pneumoconiosis and chronic bronchitis

Fig 2 indicates that the relationship throughout the whole range of values can be adequately described for practical purposes by a straight line (r = 0 998) However the tendency for the scatter to increase at the higher values of F E V suggests that a logarithmic relationship would give a better indication of the range of accuracy of conversion that can be attained Fig 3 shows the least-squares regression fitted to the logarithms of the F E V values, and 95% fiducial limits, for predicting the F E V$_{1\ 0}$(y) from the F E V$_{0\ 75}$(x)

Also shown is the simple linear regression

$$y=1\ 08x+0\ 09,$$

which it will be seen lies within the 95% limits and will lead to perfectly acceptable values at all points in the scale

The same is true if the linear regression

$$x=0\ 92y-0{\cdot}07$$

is used to predict the F E V$_{0\ 75}$ from the F E V$_{1\ 0}$

Thus we may predict the F E V$_{1\ 0}$ from the F E V$_{0}$ simply by taking 108% of the latter and adding 0 09 litre to it Similarly the F E V$_{0\ 75}$ can be predicted from the F E V$_{1\ 0}$ by taking 92% of the F E V$_{1\ 0}$ and subtracting 0 07 litre

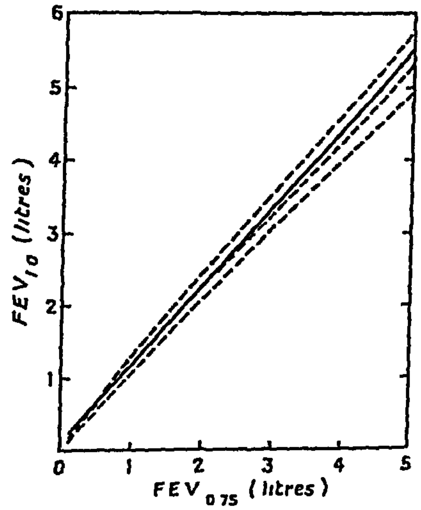

Fig 3—The relationship between F E V$_{0\ 75}$(x) and F E V$_{1\ 0}$(y) Continuous line: Linear regression $y=1\ 08x+0\ 09$ Broken lines: Logarithmic regression $y=1\ 191x^{0\ 931}$ with 95% fiducial limits

Since this work was done Miller et al[4] have published data on the relationship between the forced vital capacity and F E V$_{0\ 5}$, F E V$_{0\ 75}$, and F E V$_{1\ 0}$ From these it is possible to calculate approximately the relation between the F E V$_{0\ 75}$ and F E V$_{1\ 0}$ and this agrees well with our findings

The F E V Test

The spirometer bell is fully depressed and the movable pointer set to about 0 5 litre (The exact figure is immaterial provided it is less than the F E V measured) The seated subject is asked to inspire maximally, then to place his lips firmly around the mouthpiece, and to blow as hard as possible There is good evidence that the first and perhaps second attempts tend to be low compared with the subsequent ones, and it is therefore advisable to allow the subject two trial blows and then to average the following three consecutive ones provided they are technically satisfactory If desired each breath can be followed through to maximal expiration to obtain the vital capacity although this adds considerably to the fatigue of the test If the vital capacity is not measured, no more than half a minute's rest need usually be allowed between blows A nose clip is unnecessary

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The apparatus and calibrating device were developed in the Research Unit's workshops by Mr F Hyett, to whom we are grateful for many suggestions The instrument is now obtainable complete from D Poulton & Son, 19, Tan-y-fron, Garden Suburb, Barry, Glamorgan Our thanks are also due to Mr P D Oldham for statistical advice and to Miss Pamela Edwards for technical help

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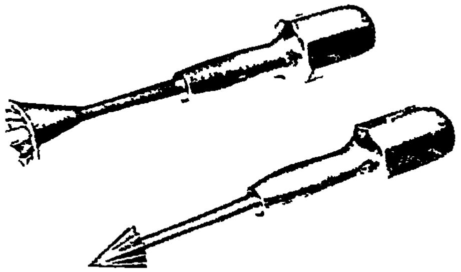
A REAMER AND BURR FOR ARTHRODESIS OF THE METATARSOPHALANGEAL JOINT

These instruments are designed to facilitate arthrodesis of the metatarsophalangeal joint of the hallux in cases of hallux valgus and hallux rigidus After exposure of the joint the metatarsal head is shaped into a conical peg by means of the specially designed reamer Preliminary shaping with an osteotome or bone-cutting forceps may be required when the joint surfaces are hard and eburnated The base of the proximal phalanx is then hollowed out with the large burr The reamer and burr are complementary, allowing the shaped metatarsal head to be jammed into the hollowed-out base of the proximal phalanx, and thus impacting the two bones firmly together Firm fixation is obtained from a screw inserted obliquely across the joint



These instruments have been produced for me by Messrs Down Bros and Meyer & Phelps Ltd., 32, New Cavendish Street, London, W 1, and the London Splint Co , 67, Weymouth Street, London, W 1

G A Marin
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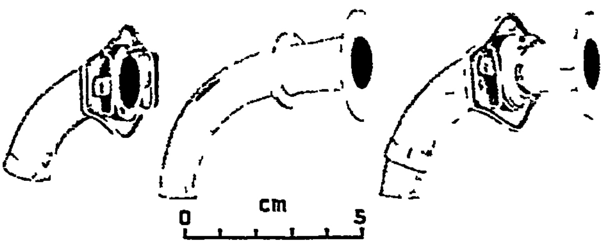
A MODIFICATION OF THE COLLEDGE LARYNGECTOMY CANNULA

During the first days after operations involving total laryngectomy the patient has to wear some form of rigid tube in the tracheostome to ensure a clear airway and give proper access for suction and toilet A detachable inner component is essential to facilitate frequent cleaning without removal of the outer tube and dressings

Since such a tube should extend forwards well clear of the inevitable heavy dressings, it usually has two perforated flanges set at right angles to the lumen The first of these is attached to the tube at skin level, being kept in position by tapes, and the second is at the upper end to prevent dressings from falling across the orifice For about 36 years these requirements have been met in this country by the Moure's modified or extended type of Lombard laryngectomy cannula But, by reason of its weight, length, and rigidity, this tube is unsatisfactory for continued use once the dressings are discarded When a laryngectomy tube is required at this or any later postoperative stage, the shorter, lighter, and more suitable Colledge laryngectomy cannula is generally used



Although satisfying basic requirements, the extended Lombard cannula is open to criticism because of its relative weight, single size, small calibre, and rigidity The conical base at skin level was perhaps originally designed with the idea that constant pressure on the healing suture line would produce ultimate dilatation of the tracheal orifice But the reverse effect may readily be produced, the pressure delaying healing at the mucocutaneous junction, with consequent fibrous contracture of the tracheal orifice

In view of these disadvantages, and for the sake of economy and simplicity, it is useful to equip one of the three existing sizes of the Colledge cannula with an inner component, thus forming a composite laryngectomy tube The inner component can be extended at either end to keep the airway open during the immediate postoperative period, when heavy dressings and frequent cleansing of the tube are essential As soon as the sutures are out and dressings are no longer required, this inner tube may be discarded, and after a further short interval the outer tube may also be dispensed with in many patients

To meet these requirements a flanged silver-alloy inner component, extended at both ends, has been designed to fit the standard medium size Colledge laryngectomy cannula (see figure) As shown, the cannula has also been fitted with a rotating catch on its upper margin to hold the inner component in place This catch is not essential since an elastic band or strip of tape may be used to prevent the inner tube from being displaced during the short period of heavy neck dressings

Specifications (for the medium size Colledge cannula) are

Weight of whole composite tube	1½ oz (2 oz *)
Length of inner tube	8 8 cm (9·0 cm)
Length of outer tube	5 5 cm. (8 9 cm)
Length of tracheal extension	1 1 cm (0 1 cm)
Length of surface extension	2 2 cm (1 5 cm)
Smallest internal diameter of inner tube	1·0 cm (0 8 cm)

Thus the composite Colledge tube is lighter and has a wider lumen than that of the Moure/Lombard pattern A similar inner component has also been manufactured to fit the small size Colledge cannula, which is more suitable for women This smaller model reduces still further the weight and bulk without impairing the efficiency of the airway

The only practical points which have emerged from a thorough clinical trial are that the airway must be carefully watched when the inner tube is changed or cleaned, and that care must be taken to see that the inner tube is always fully inserted and secured Attention to these points presents no great difficulty provided that the nurses are well trained in the postoperative management of such cases

It is hoped that this inner component for the Colledge laryngectomy cannula will give a better airway with better healing of the tracheostome, greater comfort to the patient, and possibly more economic use of existing equipment

Messrs Down Bros and Mayer & Phelps, Ltd , 32, New Cavendish Street, London, W 1, manufacture the inner component in the two sizes quoted

H J Shaw
M A., B.M. Oxon F R C S

Institute of Laryngology and Otology,
Gray s Inn Road, London, W C 1

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* Figures in parentheses are from the Moure Lombard cannula for comparison.

Reviews of Books

A Textbook of Surgical Physiology

R A JAMIESON, M B, F R C S E, surgeon, Vale of Leven Hospital, A W KAY, M D, F R C S E, professor of surgery, University of Sheffield Edinburgh E & S Livingstone 1959 Pp 623 55s

HERE is a sign of the times—a sign which will not be missed by the new generation now reaching surgical maturity—for the fact that this book has been written is an acknowledgment of the shift in basic surgical outlook. Anatomy and the topography of technique are now less important for the surgical trainee than the repercussions not only of disorder but also of his own interventions It could be argued with some justice that he who knows physiology intimately is safer than the expert in anatomy there can be no guessing to make up for ignorance of biochemical principles when applying intravenous therapy, for instance, whereas the man who has to go down an unknown lane on a dark night at least has the opportunity of finding his way with the aid of a torch This book is therefore of considerable importance since it has no exact forerunner, the information it contains could be gleaned from many sources, but it has not previously been brought together in this way The conception of the whole work is as striking an achievement as its execution

The temptation to include more than is immediately necessary for the practice of general surgery must have been considerable, but the authors have avoided it, and because the emphasis is on general surgery ovarian physiology, except in the relationship of its hormones to breast cancer, is omitted, as is the central nervous system For the same reason, no doubt, readers are referred in a useful chapter on the heart to original sources for intimate details of heart-lung machines, though the mechanical principles of the artificial kidney are described succinctly but adequately in a later chapter on that organ The style is brief and to the point, the cover comprehensive, the authors' apologies for inadvertent omission seems to have been superfluous They have done a neat job and a fine work has now been added to others which have emanated from Glasgow to make surgical study more rational, and it is pleasing to note the credit given by the authors to the man who has done much to bring this about—Prof C W Illingworth

Heavy Metals and the Brain

JOHN N CUMINGS, M D, F R C P, professor of chemical pathology in the University of London at the Institute of Neurology Oxford Blackwell Scientific Publications 1959 Pp 161 32s 6d

THIS book is arranged in three sections the first and largest is concerned with copper and hepatolenticular degeneration, and the other two deal with the nervous manifestations of poisoning by mercury and lead Its thoroughness is indicated by the fact that, of the 150-odd pages of text, no less than 30 are devoted to a bibliography of some 900 references Such a flood of references is a handicap to smooth literary composition, but the book is nevertheless highly instructive Morbid anatomy and what might be called " gross chemical pathology " are fully described, together with clinical and therapeutic data Less attention is given to biochemical mechanisms at the cellular level, and some general aspects of the relation of heavy metals to enzymes might have merited inclusion Professor Cumings has undoubtedly provided an excellent source-book on the topics he has chosen

Atlas of Roentgenographic Measurement

LEE B LUSTED, associate professor of radiology, University of Rochester School of Medicine, THEODORE E KEATS, professor of radiology, University of Missouri School of Medicine Chicago Year Book Publishers London Interscience Publishers 1959 Pp 176 68s

EXPERIENCED radiologists base their judgment largely on appearances, but the statement that " it appears normal " often seems lame and unconvincing to clinical colleagues and students This atlas aims to help radiologists in such circumstances The authors have tabulated from published data and from their own work, the average size and normal variation of most of the measurable body structures Amongst the more useful features are measurements of the cerebral ventricles and the position of the cerebral vessels as seen by arteriography The relationships of all the major joints should prove particularly valuable, especially when assessing congenital subluxation of the hip and abnormalities around the ankle-joint The text includes the standard radiographic positions by means of which such measurements can be made Many pages are devoted to the various measurements of the heart, female pelvis, and fœtal head, and there are excellent tables on the maturation of the skeleton

Fear, Punishment, Anxiety and the Wolfenden Report

CHARLES BERG London Allen & Unwin 1959 Pp 120 20s

ONE of the late Dr Charles Berg's exceptional gifts was his ability to explain difficult concepts in terms that ordinary people could follow, and this despite the fact that many of the things he understood well are rather apt to provoke resistance in readers The four essays in this book are of his usual high standard The first is a critical evaluation of that part of the Wolfenden Report which deals with homosexuality In terms of great severity, he criticises both the methods and some of the conclusions of the committee Resignations, minority reports, and reservations, all taken as disagreement amongst themselves, are explicable to the analyst only as the inevitable result of personal ignorance But some of the recommendations are praised and the fact that the committee has shed a great deal of light into dark places is acknowledged

Berg's second essay, on the psychology of punishment, is an admirable contribution, in which punished and punisher are discussed in terms of the unconscious forces that shape belief and conduct We trace the footsteps of the Roman citizen enjoying the spectacle of criminals being thrown to the lions, or being publicly castrated, down to the present day with its emphasis on psychological suffering and find it is we ourselves who stand in the Roman's shoes " Punishment *means* destruction why delude yourselves " the author asks disturbingly

The last third of the book is devoted to an attempt at understanding the nature of anxiety and fear This makes harder reading and is rather speculative in places The whole book is interesting and rewarding, not least for those whose chief concern lies outside present psychological thought

Honour a Physician

PHILIP AULD London Hollis & Carter 1959 Pp 270 16s

IN form an anecdotal narrative, this book is in effect a bitter and sustained indictment of the National Health Service as a corruptor, primarily of patients, secondarily of doctors, and a destroyer of family doctoring, good clinical medicine, and continuing medical care It has long been known that some citizens are devoid of citizenship and respect for truth and that a minority lack manners or decency of any kind The indictment's chief count is that to these people has been given the right to demand visits of their doctors at any hour of the year without cost to themselves or penalty for abuse The doctor's only remedy is to have incorrigible offenders removed from his list, thereby dumping them on his neighbours Gluttony for certificates and medicines is stimulated, good patients become shy of seeking the help they need

" Dr Gatwood " has a social and a medical conscience, his heart is in his job, he welcomed the Service, but ten years of buffeting at the hands of patients, without help or recognition of his plight by Ministry, Parliament, Press, or B M A , drives him, reluctant, out of the Service into part-time industrial medicine and private practice Some of his colleagues beat less honourable retreats

The book demands earnest attention by the profession and by those in authority over the National Health Service, for the picture it paints is one that many people believe to be truly drawn.

THE LANCET

LONDON 16 JANUARY 1960

Toxæmia of Burns

EXTENSIVE burning is followed by serious illness and, despite advances in therapy, many patients still die The general effects are so profound that it is not surprising that an embracing concept of toxæmia or autointoxication was put forward many years ago The idea is said[1] to have originated in 1876 in Petrograd, where AVDAKOFF reported that the blood of burned animals was toxic to others Toxic products released from the burned skin or the blood are alleged to produce illness and even death, but the number and variety of the toxins isolated from time to time (toxalbumin, ptomaines, formic acid, ammonia, proteoses, peptones, histamine, methyl guanidine, hydrocyanic acid, and many others) indicates either their multiplicity or their elusiveness At one time the concept led to the treatment of burns by tanning, which, by precipitating the proteins in the altered skin, was said to prevent absorption of their "toxic" products, but the tannic-acid treatment itself produced toxic effects, and tanning—or at least tannic acid—is now discredited The concept of autointoxication held the field for over fifty years, but during the last twenty to thirty of these years it lost much ground, mainly because advances in physiological and pathological knowledge of burns have rendered the theory less and less necessary and have led to the introduction of life-saving therapy—especially plasma-transfusion, antibiotics, and skin excision and grafting

The main facts about the hæmodynamic nature of burn "shock" and its relation to oligæmia have now been established Oligæmia is brought about mainly through the loss from the blood into the acutely inflamed burned area of large quantities of a plasma-like exudate, the redistribution of body-water is associated with changes in proteins and electrolytes which can lead to hypoproteinæmia, sodium depletion, and dehydration, renal failure and changes in the kidney are due to a lowered filtration-rate and renal ischæmia, and are accentuated by hæmoglobinuria, the hæmoglobinuria is due to acute red-cell destruction which produces red-cell oligæmia and anæmia and occasionally hæmolytic jaundice, whilst biochemical and metabolic disturbances involving carbohydrates, nitrogen, minerals, and vitamins are brought about by humoral or neurohumoral mechanisms in which the adrenal gland and especially adrenocortical hyperactivity are involved The burned skin rapidly becomes contaminated with bacteria of which *Streptococcus pyogenes*, *Pseudomonas pyocyanea*, *Staphylococcus aureus*, proteus, and various coliform bacilli are the most important, transient or intermittent bacteræmia is common, and not uncommon are septicæmic invasion and pneumonia, these are often responsible for "toxæmic" pyrexia, illness, and death, particularly in those surviving the first few days Nevertheless there is still no complete explanation of many effects of burning, such as the early hyperæmia of the lungs, stomach, bowel, kidneys, and other organs, early hyperpyrexia, and polypnœa, and many patients still die despite energetic medical and surgical therapy Although nearly all very extensively burned patients can be kept alive for a week or longer by modern fluid therapy, some die later—generally from pneumonia, other bacterial infection, or other causes which are sometimes obscure. Are some deaths due to non-bacterial toxæmia?

If burn toxæmia is real it is certainly a less embracing cause of illness and a less important cause of death than was once believed Experimental findings are voluminous but conflicting Severe illness or death in normal animals has been observed after injection of extracts of burned skin or exudate[2–4] or the blood or serum of burned animals,[5–7] but other workers[1 8–11] have found no deleterious effects Some of these reports are likely to be invalid because there is doubt about the sterility of the material injected and bacteria may have been responsible Cross-circulation experiments[12–15] between burned and normal animals in which the normals became ill or died do not necessarily denote that a toxin was transferred from one animal to the other, because oligæmia in both animals could explain the results, while the beneficial effects of exclusion by ligation or excision of the burned part soon after burning[1 14 16 17] can just as well be explained by the prevention of gross burn œdema and consequent oligæmia Nevertheless various substances are undoubtedly released or newly formed after burning[18] These include hæmoglobin, potassium, nuclear nucleoprotein,[19] adenosine,[20–22] phosphate, and pentose, probably ribonucleic acid, abnormal proteins[23] including gelatin,[24] polypeptides (some with leukotaxic properties[25]), histamine,[24 26 27] and glycoprotein[28] Some of these are formed in or released from the burned skin and were detected in the skin or the local œdema fluid or the lymph draining the burned area, while others are released from heat-altered red cells The liberation of a skin proteinase[29] by heat-injured epidermis, the activation of other proteolytic enzymes,[30] and the release of peptidases[31] probably account for the proteins in the exudate Skin proteinase, polypeptides, and possibly other products may play a chemical intermediary part in producing, or (as SEVITT[32] suggested) more likely maintaining, the œdema of burns

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The idea of toxæmia is being kept alive through the work of SIMONART, GODFRAIND, and their colleagues in Belgium, ROSENTHAL and his colleagues in the U S A , and FEDEROV and his colleagues in the U S S R SIMONART, whose work dates back to 1928, has summarised his experience[33 34] In laboratory animals he divides the course following burning into three overlapping phases (1) *choc circulatoire precoce* (from generalised capillary dilation), (2) *déshydration*, and (3) *autointoxication*, which he believes is due to absorption of hydrolytic products of protein in the œdema fluid Not only was œdema fluid found to be toxic or lethal after injection, but various fractions extracted from the fluid, including euglobulin and peptones, had toxic or lethal effects That œdema fluid from burned rabbits is toxic to normal rabbits was established by WILSON et al[4] in Edinburgh in 1936 and was later confirmed by CULLUMBINE et al[35] in Manchester, but the lethal intravenous dose for rabbits was as much as 10 ml of exudate per kg body-weight, and for mice it was still more[36]

The work of SOL ROSENTHAL (not to be confused with SANDFORD ROSENTHAL, who also works on burns) dates back to 1937, and he too has summarised his latest work[37] Diffusates from burned skin, obtained both in vitro[24 26] and in vivo,[37 38] were studied

The in-vivo diffusate (œdema fluid) contained protein, protein split-products, sugars, salts, histamine, bradykinin, adenyl compounds, and other substances Injection of the fluid obtained from the burned skin of rats was lethal to other rats and to mice, and the speed of dying depended on the dose and route of administration The toxic property was heat-stable, dialysable (i e , non-protein) and partially precipitated by 80% ethyl alcohol, the toxic dialysable fraction contained peptides, polynucleotides, hexoses, and pentoses Histamine, bradykinin, and adenyl compounds were not related to this burn " toxin "

Thus both the Belgian and the American work on burn œdema supports the concept originally put forward by PFEIFFER[6 7] that toxæmia is due to the formation of degradation products of proteins If this is correct, and if proteins and local products of proteolysis also play a part in producing burn œdema, then the pathogenesis of burn inflammation is closely linked to the origin of toxæmia Of course the agents concerned would not be specific for burns, similar " toxins " would be formed in any inflammatory condition of the skin and probably other tissues, and the " toxæmia " would be a general disorder This would be an important link between, on the one hand, burn inflammation and toxæmia, and, on the other hand, peptides and serum-proteins which have been reported to act as chemical mediators of altered capillary permeability in other forms of experimental inflammation[39–44] Whether the toxicity of œdema fluid found experimentally is clinically important depends on whether the toxic products enter the circulation (this seems likely), how quickly they enter, how and how quickly the body deals with them, and their rate of destruction and elimination Experimentally, it is important to establish whether in-vivo inhibition of local proteolysis by drugs or other means can reduce the toxicity of œdema fluid

The work of FEDEROV[45 46] and his colleagues in the U S S R is different They have extended the search for toxins into the interesting field of autoimmunisation Autoimmunisation might explain certain obscure features, such as delayed eosinophilia after burning,[47] which might result from sensitisation following the absorption of altered proteins in the burned area FEDEROV holds that the body is flooded with antigens derived from the burned skin and that this is responsible for part of the burn illness, and that the subsequent autoimmunisation is a regular sequel of burning Certain antigens found in the blood and tissues of burned dogs were serologically similar if not identical with those in the burned skin, they were present in the circulation one or two days after burning and were detectable for up to fifteen days Skin antigens in blood were detected by immunisation of normal guineapigs with the serum of dogs taken at various times after burning Antibodies developing in guineapig serum after absorption of the serum with dog serum removed before burning were identified, using extracts of burned dog-skin as the source of antigen Autoantibodies appeared in the circulation after the antigens had disappeared, and this raises hopes for therapy Complement-fixing titres of the order of 1 in 640 were found for saline extracts of burned skin six or seven weeks after burning The serum from dogs which had recovered from burns produced beneficial results in other burned dogs Moreover the sera of healthy dogs previously injected with blood from recently burned dogs (presumably containing skin antigens) had a pronounced therapeutic effect apparently greater than that of serum from non-immunised animals Serum from convalescent burned patients given in doses of 250 ml daily for three or four days to recently burned patients (as a supplement to other intravenous therapy) was said to have clinically impressive results FEDEROV believes that the sera injected were immune sera containing antibodies against toxic antigens liberated from burned skin, and that the protective effect was partly or largely due to neutralisation of the flood of toxic antigens Some of the beneficial effect may be due merely to the injection of serum per se or to its containing antibacterial antibodies arising after infection of the burn Obviously confirmation and further work are necessary because of the hope of improving therapy and of saving some of those who at present succumb to extensive burns

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Dental Caries

IN a Bill of Mortality for London for one week in August, 1665, the cause of 118 deaths is given as " Teeth ",[1] and for the whole of that year no less than 2614 deaths were ascribed to " Teeth and Worms "[2], but as this was during the Great Plague, when endeavours were often made to conceal the true cause of death, the diagnoses are unlikely to have been particularly accurate Dental caries is not in fact a killing disease, and research into its pathology and prevention has no dramatic appeal Nevertheless it is responsible for much suffering, loss of working-time, and, quite possibly, chronic ill health[3] The principal school dental officer for Derbyshire said recently " Already there are children in the older age groups of school who are toothless and wear full sets of dentures, while hundreds more will be in a similar condition in a year or two after leaving school "[4] And efforts at prevention are not always rational when, as **TOLLER** ruefully observes,[5] films directed at the iniquity of eating the wrong foods between meals are shown to schoolchildren on projectors bought out of the profits of the school tuck-shop

On the pathology, **DARLING**[6] makes it clear that, despite a fair amount of agreement about many of the processes in the development of caries, we do not fully understand what takes place and the reasons It is a tribute to W D **MILLER** that his " chemicoparasitic " hypothesis, first described in 1890,[7] is still accepted with slight modifications that concern mainly the role of the dental micro-structure There can be little doubt that caries is predominantly a local process although systemic factors can affect the tooth structure during development, they are not likely to produce any change in the enamel after eruption Similarly, while the composition of the saliva may have some slight effect on the process of decay, it is unlikely to exert more than a modifying influence Caries originates in the bacterial fermentation of refined carbohydrates retained in stagnation areas around the teeth, and this fermentation produces some agent that attacks the enamel What this agent is has not been determined—it could be an acid, a substance causing proteolysis, or a chelating agent A proteolytic substance seems to be the least likely of the three, since proteolysis has not been demonstrated until fairly late in the carious process There is, however, a good deal of evidence that lactic acid may be responsible Lactic acid is found in stagnation areas, carious enamel contains an abnormal amount of lactate, dilute lactic acid will produce lesions resembling those of natural caries, and lactic acid can act as chelating agent

Dental caries is a complex process—rather is it a chain of processes determined by several factors In theory the elimination of one of these factors should interrupt the sequence, but in practice no one method has prevented caries completely The great significance of the accumulation of refined carbohydrates in the stagnation areas around the teeth has been shown by **GUSTAFSSON** et al in Sweden[8] The oft-expressed opinion that one specific organism is responsible for carbohydrate fermentation in the mouth seems to be untenable (and certainly this did not form a part of **MILLER**'s original hypothesis) *Lactobacillus acidophilus* is found in association with caries, but the disease has been produced artificially both with a streptococcus and with an enterococcus The importance of the structure of the tooth was almost neglected until the publication in 1934 of the work of **MELLANBY**,[9] which showed a connection between minor enamel hypoplasia and the incidence of caries The structure of enamel is still imperfectly understood, but it exerts a great influence on the development of caries Properly developed enamel has a highly resistant surface zone, some 30 μ thick[10]—which is important in prevention, since this zone may easily be abraded during conservative treatment of adjoining teeth

Caries in the enamel progresses by selective decalcification, certain parts of the micro-structure being attacked first, and at present the only reasonable explanation seems to be that this is associated with the distribution of soluble and insoluble proteins in the enamel About equal amounts of each type of protein are present in the interprismatic spaces,[11] and the soluble protein is assumed to be the first part of the tooth substance to disappear The situation is now complicated by the work of **HELMCKE**,[12] which suggests that the interprismatic spaces may be optical illusions From electron microscopy of enamel he concludes that these spaces are produced by the refraction of light along the optic axes of the hydroxyapatite crystals forming the prisms Since it is highly improbable that these axes would all be parallel, the resulting system of optical lenses could produce—in a light microscope—the appearance of dark areas which do not in reality exist

To quote Professor **DARLING** " If we are to prevent caries we must seek to break the chain of processes which cause the lesion " Of the various means available to the dentist, none is wholly effective Stagnation of food around the teeth can be reduced, but not eliminated, by intelligent and efficient brushing To induce patients to reduce their intake of refined carbohydrate is very difficult, but something can be achieved by limiting the intake of carbohydrates strictly to mealtimes, and to the half-hour immediately afterwards, provided this is followed by attention to oral hygiene Antiseptics can render the mouth almost sterile for short periods, but are soon dispersed and diluted by the saliva Artificial immunity has been produced but is only ephemeral Enzyme inhibitors have been tried,[13] apparently with some initial success, but little has been heard of them in the past decade A more promising, though empirical, method is the administration of pyridoxone (vitamin B_6)[14], but this has not yet been established as a practical means of control The neutralisation of lactic acid as it is formed presents the same difficulties as in making the oral cavity sterile it is almost impossible to modify the composition of the saliva Rendering the soluble protein of the enamel insoluble might prevent a great deal of caries—a possibility which is now being investigated The use of silver nitrate has little scientific backing, and yet clinical experience shows that it is often effective

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[1] Haggard H W Devils Drugs and Doctors, p 192 New York, 1929
[2] Gale A H Epidemic Diseases, p 151 London 1959
[3] See *Lancet* 1951, i 1009
[4] *Times*, Sept 11, 1959
[5] Toller, J R Memorandum to City of Cambridge Education Committee Dec 10 1959
[6] Darling, A I *Brit dent J* 1959 107, 287
[7] Miller W D The Micro-organisms of the Human Mouth Philadelphia, 1890
[8] Gustafsson, B E , Quensel, C-E , Lanke, L S , Lundqvist, C , Grahnen, H Bonow B E , Krasse, B O *Acta odont. scand* 1954 11 232
[9] Mellanby, M *Spec Rep Ser med Res Coun , Lond* 1934, no 191
[10] Applebaum D *J dent Res* 1932, 12, 619
[11] Stack, M V *J Amer dent Ass* 1954, 48, 297
[12] Helmcke, G *Umschau* 1959, 17, 516 Cited by *New Scientist*, 1959, 6, 709

But neither the ramifications of research nor the skilful expedients of dentistry should distract attention from the most important fact about caries—that it is a consequence of malnutrition and that we already know enough to prevent nearly all of it In his fascinating review of the changes in its incidence and distribution in this country throughout the ages, HARDWICK[15] relates these to changes in our diet, which have been greater in the past hundred and fifty years than ever before When a disease goes up and down with alterations in feeding, it is obviously a soluble problem of public health, and, though HARDWICK is not prepared to say which of the many nutritional alterations of the 19th and 20th centuries is chiefly responsible for caries, he shows that all the more likely factors are related to refining of foods Most conspicuous, perhaps, is the loss of most of the components which promote mastication and natural cleansing of the teeth Next there is the large consumption of refined sugars, which (together with heating of our homes and lessening of our physical activity) has reduced the intake of old-fashioned foods containing possibly protective factors such as vitamins and trace elements Likewise the concomitant modifications of the processing of flour "have been followed by marked changes in caries activity" Changes in the incidence of the disease during and after the two world wars suggest that there are (or should be) factors in food whose absence during a tooth's formation makes it susceptible to caries later "An increasingly large group of research workers believes that these protective factors are of an inorganic nature and it has been suggested that caries may be a trace element deficiency disease"

The day may be far distant when the public can be weaned from its present somewhat infantile overdependence on refined sugar and fat indeed there are hardly any signs yet that doctors and dentists care enough about nutrition to set their weight firmly against the commercial interests concerned Meanwhile, though perhaps a pis-aller, the correction of fluorine deficiency seems to be our most hopeful objective Where water-supplies are clearly below normal in fluorine content, any reasonable person should be willing to accept the minute addition of fluoride needed to make up for the geological lack Doing no more than this has sometimes reduced the local incidence of caries by as much as half

Annotations

FERTILITY CONTROL

IF man's most pressing task is to escape total destruction by nuclear warfare, the next most urgent is to feed and clothe his ever-increasing family[1] Economists since the days of Malthus have insisted that measures to increase food production are bound to prove increasingly ineffective as time passes Fertility, according to this viewpoint, must be controlled, though without prejudicing the health and welfare of the individual or the race This simply stated goal is proving difficult to attain—a fact that testifies to the long course of evolution in which mammals have been developing means for protecting sex cells and embryos from environmental interference

Reproduction can be blocked in broadly two ways by preventing the production and union of sex cells, and by bringing about, directly or indirectly, the death of the embryo It is now agreed that ideally contraception should be applied by oral administration of the active agent, and specifications for an ideal contraceptive have been drawn up[2] Some of the latest products of the search for a suitable agent were discussed by Dr H Jackson in an address to the Pharmaceutical Society on Dec 3

Dr Jackson is well known for his studies on several groups of organic compounds, notably the ethyleneimino derivatives, one of which is tretamine (T E M) Administered in a single moderate dose to male rats, this damages the late spermatids but not the earlier spermatogenic cells nor the maturing spermatozoa As a result, the rats become sterile between the 20th and the 26th days after treatment, though they are fertile before and after this period At higher dose levels, the damage extends to other stages of spermatogenesis, involving spermatogonia and maturing spermatozoa[3–5] Similar results have been obtained with mice[6] The action of tretamine, besides being remarkably cell-specific, is notable in that it renders the epididymal spermatozoa infertile without inhibiting their motility or their ability to reach and enter the eggs

Another group of compounds discussed by Dr Jackson was the sulphonoxalkanes, such as busulphan ('Myleran') Here again, damage tends to be concentrated at specific stages of spermatogenesis with busulphan on the spermatogonia, with chloroethylmethanesulphonate on the spermatids and spermatozoa, and with dimethylmyleran on both groups of cells[4] With these and other compounds of the same family, it is evidently possible to build up a "spectrum" of activity, wherein variations in effect accompany relatively small differences in chemical structure These drugs can yield precise data on the course of spermatogenesis and on the physiological and chemical peculiarities of the spermatozoon But whether they can suitably be applied to the control of fertility in man is another matter, for they are known to be capable of producing changes in the genetic material of the spermatozoon,[6, 7] and for other reasons, too, may be classed as radiomimetic agents [8] Substances which have these effects, but which do not prevent the spermatozoon from entering the egg, cannot be regarded as any less hazardous than atomic radiation and should be treated with the same reverence

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[13] Fosdick L S Calandra J C *J dent Res* 1947, 26, 309

[14] Strean L P, Bell F T Gilfillan E W, Emerson, G A, Howe, E E *N Y St dent J* 1958, 24 133

[15] Hardwick, J L *Brit dent J* Jan 5, 1960, p 9

[1] See *Lancet*, 1959, ii, 349

[2] Parkes A S *Proc Soc Study Fertil* 1953 5 20

[3] Bock M, Jackson H *Brit J Pharmacol* 1957, 12, 1

[4] Jackson, H, Fox B W, Craig A W *ibid* 1959 14 149

[5] Steinberger E, Nelson, W O, Boccabella, A, Dixon W J *Endocrinology*, 1959 65 40

[6] Cattanach, B M Edwards, R G *Proc roy Soc Edinb* B, 1959, 54

Dangers of somewhat lower degree, though still serious, attend practices that depend on destruction of the early embryo Here, too, phenomenal specificity of chemical action is manifest, notably in the lethal effect of the triphenylethanol derivative known briefly as MER-25 on the unimplanted embryo [9] and that of podophyllotoxin after implantation [10] This work represents a fascinating aspect of experimental biology, but there is an ever-present risk that the embryos may not all be killed and that damaged embryos may survive to term

Some lines of research seem to offer hopes of satisfactory results with comparative safety these depend on suppression of ovulation or of implantation The best known is the oral administration of certain 19-nor steroids with progestational activity which apparently inhibit the gonadotrophin output from the pituitary [11] Hopeful also are the results with *m*-xylohydroquinone [12, 13], this substance is believed to inactivate gonadotrophin, œstrogen, and progesterone in vivo by combining directly with them In the suppression of implantation, some success has been reported in rats treated with ergotoxine,[14] but the most innocuous method of achieving this effect has recently been observed in mice pregnancy was interrupted at high frequency by no more drastic an expedient than allowing the females to become aware of the proximity of strange males [15, 16]

TREATMENT OF INFECTIONS IN HOSPITAL

IN the past twenty-five years sulphonamides, penicillin, antituberculous drugs, broad-spectrum antibiotics, various antistaphylococcal agents, and some promising antifungal substances have become available Nevertheless, infective disease remains undefeated and some types are on the increase The lamentable lack of achievement has been exposed by Finland and his colleagues [17] in an authoritative report to the Council on Drugs of the American Medical Association These workers have reviewed the changing pattern of infections observed in the Boston City Hospital in certain years, carefully chosen to reflect the changing fashion in chemotherapy The year 1935 was selected as a baseline for the pre-sulphonamide era, 1941 to reveal the impact of the sulphonamides before they had been joined by penicillin, 1947 when both penicillin and streptomycin had been widely used, 1951 to show the influence of the broad-spectrum antibiotics, and 1957 to define recent trends influenced by most or all currently available antibiotics In order to make valid comparisons, attention was restricted to septicæmia, meningitis, empyema, and necropsy material from which bacteriological studies were satisfactory

In 1935 about 300 septicæmic patients were admitted to hospital and roughly three-fifths of these died By 1957 there were twice as many septicæmic patients, nearly two-fifths of whom died whereas 2 out of 5 septicæmic patients could be saved in the dark ages before sulphonamides, no more than 3 out of 5 survive with the help of modern chemotherapy The decline in mortality occurred in the years 1935–41, when the sulphonamides were in exclusive use, for by *1941* only one-third of septicæmic patients died Since then and, with the use of penicillin, streptomycin, and the broad-spectrum antibiotics, the mortality-rate has increased

In contrast, meningitis and empyema have become rather less of a challenge As regards meningitis, there were rather more cases in 1957 than in 1935, but between these years the mortality had steadily fallen from 80% to 20% Between these particular years the number of patients with empyema had halved, although the mortality rate had risen slightly from 20 to 30%

The bacteria isolated from these infections have changed significantly over the years, and this changing flora mirrors the success and failure of the antibiotics Pneumococci and hæmolytic streptococci have continued to remain sensitive to antibiotics, but success in this direction has been offset by the increasing incidence of infection due to staphylococci, enterococci, and various gram-negative organisms, against which existing drugs are less potent. The mortality-rate of septicæmia due to gram-positive organisms was 67% in 1935 and 33% in 1957 The fall in mortality would have been far more impressive but for staphylococcal infections, whose incidence quadrupled over these years The incidence of septicæmia due to gram-negative organisms increased sixfold, and the mortality also rose slightly from 42% (1935) to 54% (1957) In essence, the antibiotic era has witnessed a change from pneumococcal to staphylococcal and coliform septicæmia The gravity of the staphylococcal menace is reflected also in the frequency with which this organism was isolated in pure or almost pure culture from one or more important sites in necropsy material It was recovered from 7% of necropsies in 1935 compared with 24% in 1957 Finland and his coworkers draw attention to this as a crude index of the increasing significance of *Staphylococcus aureus* as a cause of death

This survey might be interpreted less confidently had it not been made at the Boston City Hospital—a large general city hospital, admitting 4 patients every hour round the clock, where throughout the years covered by the survey Dr Maxwell Finland has himself been responsible for the management of infections

Possible steps to reduce the hazard of infections include vigilance against cross-infection, combination of antibiotics, rotation of drugs, limitation of the use of some, the introduction of fresh antistaphylococcal agents, and new measures to improve host resistance That the challenge has been accepted in London is evident from the painstaking work of Barber and her colleagues [15] and the cooperation of the whole staff of Hammersmith Hospital, where some reversal of antibiotic resistance in hospital staphylococcal infection has already been achieved by the introduction of some of these measures in the surgical wards At the beginning of the investigation, 70% of staphylococcal infections were resistant to penicillin and tetracycline and only 12% were sensitive

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[7] Cattanach B M *Nature, Lond* 1957, 180 1364

[8] Craig, A W, Fox B W Jackson, H *Brit J Radiol* 1959, 32, 390

[9] Segal, S J, Nelson W O *Proc Soc exp Biol, N Y* 1958, 98, 431

[10] Wiesner, B P, Yudkin, J *Nature, Lond* 1955, 176, 249

[11] Pincus, G *Stud Fertil* 1958, 10 3

[12] Sanyal, S N *J Med intern med Abstr* 1959, 23, 15

[13] Sanyal, S N, Rana M *ibid* p 33

[14] Shelesnyak M C *Recent Progr Hormone Res* 1957, 13, 269

[15] Bruce H M *Nature, Lond* 1959, 184 105

[16] Bruce H M *J Reprod Fertil* (in the press)

[17] Finland, M, Jones, W F, Barnes, M W *J Amer med Ass* 1959, 170, 2188

[18] Barber M, Dutton A A C, Beard M A, Elmes, P C, Williams, R *Brit med J* Jan 2, 1960, p 11

to penicillin At the end of the investigation, 36% of the infections were resistant to penicillin and tetracycline and 48% were sensitive to penicillin The use of penicillin was deliberately restricted, and broad-spectrum antibiotics in combination were used more freely The consumption of penicillin in the hospital was halved, but that of tetracycline, chloramphenicol, and erythromycin doubled, and the use of novobiocin increased sixfold The increased cost entailed by this programme is unimportant if it succeeds One peril is that gram-negative organisms may become increasingly often resistant to the broad-spectrum antibiotics It would be difficult to defend the unlimited use of polymyxin for bacillary dysentery and trivial skin infections in a hospital, if this involved an increase in infections with resistant pseudomonas for which originally only polymyxin is effective This organism alone was responsible for 13 deaths in 1957 in the Boston City Hospital, compared with *none* in 1935 Barber and her coworkers are well aware of this danger, and, in re-shaping their policy for the next phase of the attack on hospital infection, they might even include the coliform organisms with staphylococci as their quarry

CLASSIFICATION OF PSYCHIATRIC DISORDERS

DISCOVERING the prevalence of mental disorders in different communities helps both to throw light on their causation and to plan the therapeutic services Minor psychiatric illness is much commoner than is usually realised, both as "maladjustment" in children [1] and in adults consulting their family doctors [2], and outpatient facilities must be planned to meet the need Arentsen and Strømgren [3] have reported a survey based on a census of all persons resident in Danish psychiatric institutions on a day in the autumn of 1957 The prevalence of such patients—228 per 100,000—was considerably less than the 342 per 100,000 in this country and the 430 per 100,000 in Sweden, and this was presumed to be due to nosocomial factors rather than to differences in morbidity Sweden has been able to provide more hospital beds than Denmark and Norway (where the rate is also low), and geographical factors make outpatient management easier in Denmark Distribution of diagnostic subgroups did not, overall, differ greatly throughout the country, but diagnostic practices in certain hospitals were strikingly discrepant, reflecting the present unsatisfactory state of classification In her survey of mental illness in London, Vera Norris [4] found similar differences In some conditions the concordance of diagnosis for the same patient between observation ward and mental hospital was less than 30% Agreement on schizophrenia and manic-depressive psychosis, however, was about 70%, and the difference between the diagnoses was borne out by the very highly significant ($P < 0{\cdot}0001$) differences in duration of stay Prof Erwin Stengel [5] has surveyed 58 current classifications at the request of the World Health Organisation He found that none was wholly satisfactory and most were bedevilled by national and personal sentiment Despite minor difficulties with cardiovascular classification [6] the International Classification of Diseases has been generally accepted throughout the world except for the psychiatric section Disagreement on definition has led to gross discrepancies in use, and Professor Stengel maintains that an acceptable classification demands that grouping be exhaustive and the categories mutually exclusive with each explicitly defined That the present system has failed is made clear by Miss Eileen Brooke [5] The I C D and the American Psychiatric Association classifications are theoretically interchangeable, but when some 200 diagnoses were coded on each separately and the A P A coding was used to give an I C D code number, there was concordance in only a minority Cohort analysis of cases discharged and readmitted elsewhere within four years showed a similar minority of concordant diagnoses Miss Brooke concluded—as did Dr Norris from similar findings—that only with the broad groupings did diagnosis seem "not completely haphazard"

This unsatisfactory situation is hindering progress [7] Pending the evolution of objective indices, we can only await the outcome of W H O's endeavours and hope that the conclusions will prove universally acceptable Fortunately the planning of our future services need not wait on these deliberations, Professor McKeown and his colleagues, for example, have described a very useful system of classification, based on the treatment needs of patients, which ignores diagnosis [8] [9]

PULMONARY ARTERIOVENOUS FISTULA IN HEREDITARY HÆMORRHAGIC TELANGIECTASIA

EVERY large general hospital is certain to have on its list of frequent attenders a small group of unfortunate adults who come to the casualty department complaining of recurrent bleeding from the nose or lips or mouth The blood is seen to stem from an insignificant leak in the centre of a small ruby patch, many of which are usually to be found scattered here and there on the mucous membrane Although the flow of blood is seldom vigorous it may eventually, by its persistence, cause some concern Its arrest can certainly be infuriatingly difficult, whether it be attempted by sustained compression or by cautery, or by both Each ruby patch marks the position of a tiny arteriovenous communication at the capillary level Presumably these vessels are very close to the surface, or else they are abnormally fragile Whatever the cause, they can be induced to bleed by the most trivial of injuries

This vascular anomaly is not restricted to the mouth and nose, but may affect any portion of the skin of the trunk Similar lesions can also involve mucous membrane elsewhere, and bleeding from the gastrointestinal tract or hæmaturia often feature in the history The disease is known to be hereditary and is presumed to be transmitted as a simple dominant with equal frequency by males and females Most have now agreed to call the disease hereditary hæmorrhagic telangiectasia, but some students and compilers of texts still delight in the eponymous prolixity of Rendu-Osler-Weber disease

Arteriovenous shunts in the lesser circulation, between branches of the pulmonary artery and of the pulmonary vein, were recognised at necropsy at the turn of the century, but it was not until 1939 that the first case was diagnosed clinically [10] The triad of cyanosis, polycythæmia, and clubbing, which are the clinical features of the more serious shunts, is now widely recognised Only in more recent years has it been widely appreciated that the great majority of patients with pulmonary arteriovenous fistulas will be found on careful examination to have, in addition, the characteristic lesions of hæmorrhagic telangiectasia Purnel and Muras [11] in an analysis of 170 reported cases found that, of 102 patients concerning whom full information was available, 70 had cutaneous telangiectasia and that in close on 60% there was a family history of the disease It seems clear, therefore, that we must now regard pulmonary arteriovenous fistulas not as localised lesions but as part of a general vascular anomaly, and that we must for this reason seek out other vascular deficiencies in seeking supporting evidence of a pulmonary arteriovenous shunt

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[1] Ministry of Education Report of the Committee on Maladjusted Children, 1955

[2] Shepherd M Fisher, M , Stein, L , Kessel, W I N *Proc R Soc Med* 1959, 52, 269

[3] Arentsen K , Strömgren, E *Acta jutlandica* 1959, 31, 1

[4] Norris, V Mental Illness in London Maudsley monograph no 6, 1959

[5] Stengel, E Address at a meeting of the Section of Psychiatry, Royal Society of Medicine Nov 10, 1959

[6] See *Lancet*, Nov 14, 1959, p 836

[7] *Lancet*, Aug 15, 1959 p 117

[8] Garratt, F N , Lowe C R McKeown, T *ibid* 1959, i, 682

[9] McKeown, T *ibid* 1959, i 701

[10] Smith, H L , Horton, B T *Amer Heart J* 1939, 18, 589

How many patients who present with evidence of hæmorrhagic telangiectasia have, in addition, pulmonary arteriovenous fistulas? Clagett et al [12] have now partly answered this question They studied 330 descendants of a young man who migrated from Germany to the United States in the '60s or '70s of last century, and who passed on the stigmata of hæmorrhagic telangiectasia to the generations that followed It must be a close-knit family, for no fewer than 231 of them could be traced, and of this number 40% were found to have overt manifestations of the disease When the investigation was narrowed down in a search for pulmonary arteriovenous fistulas, these were found to be present in 14 (i e, 6 1% of the family group studied) In 8 it was found in a routine X-ray, in 6 there were symptoms and signs attributable to the bypass

The finding of fistulas in such a high proportion of cases suggests that we should review from time to time all adult patients with hæmorrhagic telangiectasia, for the hazards of an uncorrected fistula can be formidable, including hæmothorax, thrombosis, and cerebral abscess Whether we stumble on this lesion or unearth it only after diligent inquiry, its operative correction in every case may not be justified The fistulas are often multiple, and it is important not to destroy too much healthy lung tissue The need for operation will be determined by the number of fistulas and by their size and location

BLOOD SAMPLES

BLOOD taken for the Wassermann reaction has proved useful for purposes besides the diagnosis of syphilis Quite frequently a pathologist who has wished to establish normal values for some biochemical estimation, or to look for antibodies to some infection in the general population, has found his evidence in the sera left over from the W R Similar use has been made of blood taken for grouping or for biochemical tests Such specimens have yielded some useful information but are far from perfect In this country at any rate, those suspected of having syphilis are not a fair sample of the population, and those whose blood is sent to the biochemist will presumably be ill Blood donors will be healthy, but there will be no children in the sample and the Registrar General's classes I and II will be over-represented To obtain a random sample fortuitously is, in fact, almost impossible Another difficulty with samples obtained by chance is the absence of useful information to accompany them the discovery of brucella antibodies is almost meaningless without knowledge of the residence and occupation of the subjects

As an improvement on the use of surplus blood specimens there is a lot to be said for the deliberate survey. The subjects can be chosen and classified on the spot. The serologist or biochemist (but rarely the hæmatologist) can collect his specimens in remote and barbarous places and examine them at leisure in a well-equipped laboratory Such surveys have already given useful results on many subjects—for instance, the distribution of antibodies to poliomyelitis and the frequency of leptospiral infections in dogs A publication from W.H O [1] contains some excellent advice and suggestions

The simplest example is the establishment of a "normal" value in a static community, but the experimenter will soon find that, though the "normal" is a common animal, it is very hard to catch Medical students and nurses are traditional normals but they represent limited age and social groups and are (or should be) the thing most hateful to the statistician—volunteers The inmates of mental hospitals and gaols are less representative of the community as a whole than might be imagined The most satisfactory sample among young adults is probably obtained from conscripted recruits to the armed services It seems that less sophisticated communities are sometimes easier to sample. One of the most profitable uses of the survey method has been in the detection of influenzal antibodies in isolated villages To judge from the published accounts the Eskimo in Greenland is far more generous with his blood than the English rustic The success of the detailed surveys by the M R C Pneumoconiosis Unit in the Rhondda Fach and elsewhere shows what sincerity and enthusiasm can do, but to obtain quite a small blood sample from a cross-section of the whole population of, say, Bournemouth would be difficult and time-consuming Electoral rolls, school registers, and registrations of births allow the investigator to select a random sample within a limited age-group with precision, though he is likely to lose up to 20% owing to natural movements of the population Persuading the subjects (and their mothers) to allow venepuncture is another matter at no age is it painless or without risk of minor damage The appeal for the general good which goes for little in the population as a whole can be a powerful weapon in a group of skilled tradesmen or an army unit. Persuasion gets a little attention in this booklet It is a subject on which the serologist might be wise to consult the psychologist.

Samples of serum can be kept for years by freezing, and W H O envisages a serum bank for use by investigators in the future The idea is attractive and has already been put into action in a small way here and in the U S.A., but we fear that its application may lead to some disappointments Asking the right question at the right time is difficult enough, but to ask the questions which will be right in ten years' time will be a near-miracle. Multipurpose blood surveys are more promising, but without doubt those which have been most productive in the past have been those with limited objectives—e g, the search for yellow-fever antibodies in Central Africa. But such surveys are neither cheap nor easy and they cause bother and discomfort to many, and anyone who undertakes them should have a clear conscience that what he does is for the general weal

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[11] Purnel, P Muras O *Thorax*, 1957, 6, 101

[12] Hodgson C H Burchell, H B, Good, C A., Clagett, O T *New Engl J Med* 1959, 261, 625

[1] Immunological and Hæmatological Surveys. Report of a Study Group *Tech Rep Ser World Hlth Org* 1959, no 181 Pp 35 1s 9d

Special Articles

INTERPRETATION OF CHROMOSOME COUNTS MADE ON BONE-MARROW CELLS

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In a number of recent reports the distribution of marrow chromosome counts have been recorded from both normal and abnormal individuals.

The technique of making the bone-marrow preparations has been described by Ford, Jacobs, and Lajtha (1958), the basic steps being the short-term culture of the marrow cells in the presence of colchicine, the treatment of the cells with a hypotonic solution, and their subsequent squashing under a coverslip. The chromosomes are then counted in suitable cells—i.e., cells in which the chromosomes are well spread and lie as far as possible in the same optical plane. It is unusual, however, for every metaphase cell selected for counting to show the same number of chromosomes, and a range of chromosome counts is recorded in which the majority of atypical cells have a chromosome number less than the modal number.

In selecting cells for counting, cells considered unsuitable are those in which the chromosomes are poorly spread, those in which it is obvious that the cell has been ruptured and chromosomes lost, and those in which the appearances of the chromosomes indicate that one or more have been split at their centromeres into their sister chromatids. It is possible to ensure that in selected cells there are no chromosomes that have been obviously split at their centromeres, but it is not possible, in selecting cells for counting, to be certain that one or two of the chromosomes have not been lost.

In preparations made from bone-marrow in which there are no malignant cells it is customary to accept the modal number as the true somatic number of the individual and to regard counts differing from this as due to the presence of artefacts. It is possible, however, that in a normal bone-marrow there may be occasional cells with a true chromosome number different from the modal number, and it is also possible that an occasional individual may be a mosaic—i.e., his body may contain two or more stem lines with different chromosome numbers. Several such presumed mosaics have been reported by Ford and his coworkers (Ford et al. 1959, Ford 1959a), —i.e., an XX/XXY mosaic containing cells with 46 and 47 chromosomes, and three XO/XX mosaics with cells having 45 and 46 chromosomes.

Our object here is to discuss (1) the meaning of the variability of chromosome counts, and (2) the conditions to be fulfilled before a presumed mosaic can be accepted as a reality. Our assessment can be no more than preliminary, since the techniques are new and the preparative standards have changed appreciably over a short period, but a review seems desirable because the significance of the reported variations in chromosome number has been misunderstood.

For example, Ford, Jacobs, and Lajtha (1958) recorded a case of pernicious anæmia in which 25 out of 70 cells examined showed chromosome counts less than the modal number of 46, and it has been inferred from this by others that true numerical chromosome abnormalities may occur in the bone-marrow of patients with pernicious anæmia (*Lancet* 1959). Subsequently Ford (1959b) pointed out that this particular marrow preparation was made at a comparatively early stage in the development of the technique, and that the variation in chromosome number was most likely to have been due to preparative faults. The data from five untreated cases of megaloblastic anæmia which we give below support his conclusion, and on present evidence there appears no reason to doubt that such patients have a normal diploid number of 46.

Material

The marrow chromosome counts have been analysed from fifty-seven patients and ten healthy subjects in whom the modal number was 46, four with a modal number of 45, and thirteen with a modal number of 47. The material was obtained from the following groups:

Modal Number 46

A. Ten healthy males and females. Several of these were studied because their children had shown chromosomal abnormalities.

B. Four patients with testicular feminisation. Data for these have been published by Jacobs et al. (1959a).

C. Fourteen patients with ankylosing spondylitis.

D. Six patients with testicular cancer, in none of whom was there any evidence of metastatic spread.

E. Seven patients with male gonadal dysgenesis in whom the nuclear sex was male.

F. Five patients with primary amenorrhœa.

G. Five patients with untreated megaloblastic anæmia.

H. Nine patients with various congenital or genetically determined conditions.

I. Seven patients with various other conditions.

Modal Number 45

J. Four patients with Turner's syndrome—i.e., female gonadal dysgenesis with a male nuclear sex and a chromosomal sex of XO. The data for one of these (H188) have been published by Jacobs and Keay (1959).

Modal Number 47

K. Nine patients with mongolism, the data for four of whom (H114, H120, H122, H125) have been published by Jacobs et al. (1959b).

L. Three patients with Klinefelter's syndrome—i.e., male gonadal dysgenesis with a female nuclear sex and a chromosomal sex of XXY. The data for one of these (H54) have been published by Jacobs and Strong (1959).

M. One patient with a female nuclear sex and a chromosomal sex of XXX—the "super-female" described by Jacobs et al. (1959c).

It will be noted that in the descriptions of the eleven cases which have been published previously, the chromosome counts relate in each instance to a larger number of dividing cells than those given in the present tables. The reason is that our practice has been to score the counted cells in two ways, distinguishing the results for those cells for which there have been no doubt about the counts from those cells for which the exact number of chromosomes is uncertain. In these latter a decision was made as to which category of chromosome number each cell was most likely to belong to, and, in the previously reported counts, both the certain and the uncertain cells have been included. In this and subsequent communications unless otherwise stated, we shall report cells only when an exact count can be made.

Results

The data for patients with a normal chromosome number are given in table I, the numbers of cells which contained less than 44, 44, 45, 46, 47, 48, and more than 48 chromosomes are shown separately. Polyploid cells were seen in many of the preparations, but these cells have been excluded because the standards required to recognise a polyploid cell are less strict than those required to determine the exact number of chromosomes in a diploid cell. The proportion of polyploid cells recorded in a count is therefore likely to be misleading, unless it is sought as a separate item

The total number of cells in each category has been summed for each group of conditions in table I, and the grand totals have been determined for sixty-seven subjects Altogether 1602 cells have been counted; of these 1362

TABLE I—CHROMOSOME COUNTS IN SIXTY-SEVEN PERSONS WITH A MODAL NUMBER OF 46

Group	Patient	Diagnosis	<44	44	45	46	47	48	>48	Total	Probability‡
A	H 79	Normal male		2	3	24			1	30	0·221
	H110	„ „		2	2	20				24	0·391
	H172	„ „	2		2	9				13	0·062
	H 83	„ female		1	2	31	1			35	0·705
	H106	„ „			2	21				23	0·786
	H111	„ „	1		1	16	1			19	0·438
	H112	„ „	2	2	1	43				48	0·806
	H129	„ „		1	1	16				18	0·648
	H159	„ „	1	3		22	1			27	0·487
	H173	„ „				10				10	0·902
Totals			6	11	14	212	3		1	247	
B	H113	Testicular feminisation	1	1	3	25	1			31	0·245
	H139	„ „	1	1	2	25				29	0·548
	H141	„ „			2	9				11	0·364
	H149	„ „			2	21				23	0·786
Totals			2	2	9	80	1			94	
C	H 1	Ankylosing spondylitis	2	1	1	16	1			21	0·140
	H 33	„ „				8	1			9	0·584
	H 42	„ „			2	5	1			8	0·063
	H 48	„ „		2	2	26	1			31	0·412
	H 49	„ „		1		21				22	0·918
	H 58	„ „		1	2	23	2			28	0·324
	H 72	„ „	2		1	20	2	1		26	0·134
	H193	„ „			3	18	5			26	0·022
	H197	„ „	1	1	1	11				14	0·249
	H201	„ „			1	12				13	0·740
	H203	„ „			1	15				16	0·821
	H206	„ „			1	11				12	0·707
	H212	„ „		1	1	27	1			30	0·764
	H216	„ „				27				27	0·994
Totals			5	7	16	240	14	1		283	
D	H 2	Carcinoma testis	1		6	28	1	1		37	0·067
	H 52	„ „	1		1	6				8	0·224
	H 55	„ „	1		2	25	1			29	0·548
	H202	„ „			1	6				7	0·481
	H208	„ „				19	1			20	0·892
	H222	„ „			2	21	1			24	0·608
Totals			3		12	105	4	1		125	
E	H 62	Male gonadal dysgenesis (−ve)*			3	9	1			13	0·062
	H 78	„ „ „ „			3	13	1			17	0·172
	H 84	„ „ „ „			1	24				25	0·945
	H 92	„ „ „ „		2	2	69				73	0·993
	H109	„ „ „ „			2	19				21	0·738
	H117	„ „ „ „	1		1	23	1			26	0·666
	H195	„ „ „ „			1	14				15	0·797
Totals			1	2	13	171	3			190	
F	H126	Primary amenorrhœa			2	26				28	0·875
	H167	„ „		1	2	5				8	0·062
	H170	„ „			2	10	1			13	0·184
	H191	„ „			1	9				10	0·629
	H194	„ „			2	14	2			18	0·200
Totals				1	9	64	3			77	
G	H 81	Megaloblastic anæmia (untreated)	2	1	6	66	2			77	0·584
	H 95	„ „ „			1	25	2			28	0·717
	H136	„ „ „			2	21				23	0·726
	H204	„ „ „			1	17				18	0·861
	H223	„ „ „	1	1		12	1			15	0·288
Totals			3	2	10	141	5			161	
H	H130	Achondroplasia	1	1	2	13				17	0·172
	H132	„		2	2	52				56	0·956
	H134	Epiloia		1	3	22	1			27	0·294
	H135	Microcephaly		1	1	14				16	0·578
	H161	„ †		1	3	22	1			27	0·294
	H164	Albright's disease	1	1		5				7	0·178
	H171	Female gonadal dysgenesis (−ve	3	2	2	26				33	0·164
	H178	True hermaphroditism	1	1		6				8	0·224
	H220	? Juvenile amaurotic idiocy	2	1	5	27	1			36	0·058
Totals			8	11	18	187	3			227	
I	H 47	Pulmonary tuberculosis				17				17	0·068
	H 60	Adrenal virilism	1	1	4	24				30	0·221
	H 75	Megaloblastic anæmia (treated)			5	24	2			31	0·245
	H 89	(„)	1		1	41				43	0·973
	H118	Hæmolytic anæmia	2	1	5	18	3			29	0·001
	H155	Infectious mononucleosis	3		3	19	2			27	0·027
	H227	„ „		1	1	19				21	0·738
Totals			7	3	19	162	7			198	
All		All patients	35	39	120	1362	43	2	1	1602	
		Percent	2·19	2·43	7·49	85·02	2·68	0·13	0·07	100·00	

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* +ve and −ve indicates male and female nuclear sex

† H161 This patient presented with short stature, webbing of neck, unusual thickening of the [illegible] a high arched palate [illegible] and [illegible] He was originally thought to be perhaps a male example of Turner's syndrome

‡ See footnote p. 162

TABLE II—PROBABILITY OF OBTAINING THE OBSERVED PROPORTIONS OF TYPICAL AND ATYPICAL CELLS IN NINE GROUPS OF PATIENTS WITH NORMAL KARYOTYPES

Group (no. of subjects)	Value of χ^2	Probability ($n=1$)
A Healthy men and women (10)	0·150	Between 0·1 and 0·9
B Testicular feminisation (4)	0·001	0·97
C Ankylosing spondylitis (14)	0·012	0·91
D Testicular cancer (6)	0·110	Between 0·1 and 0·9
E Chromatin-negative male gonadal dysgenesis (7)	4·200	0·04
F Primary amenorrhœa (5)	0·230	Between 0·1 and 0·9
G Untreated megaloblastic anæmia (5)	0·920	,, ,,
H Various congenital or genetically determined conditions (9)	1·447	,, ,,
I Various other conditions (7)	1·817	,, ,,

(85·0%) contained 46 chromosomes. Examination of the distribution of cell counts shows that the distribution is not symmetrical but is negatively skewed, and that 12·1% of cells give counts of less than 46 in contrast to 2·9% with counts in excess of 46. This greater preponderance of "atypical" cells with counts of less than 46 chromosomes is seen in all the groups and, in each of them, the most common type is a cell with a count of 45 chromosomes.

The homogeneity of the material shown in table I may be tested by comparing separately the data for each group of patients with those obtained from all the groups together. The results (table II) show that the variation in the proportion of atypical cells in each group can reasonably be attributed to chance. The most extreme variation (group E) would be expected to occur once in 25 tests. This figure must be interpreted in the light of the fact that nine groups were examined and it is reasonable to suppose that among so many groups a probability of this order would occur at least once due to chance factors alone (P = 0·44).

A more detailed analysis has also been made by examining for each patient the probability of obtaining the observed proportion of cells with modal and non-modal counts. These have been obtained from published Binomial Tables by assuming that the expected proportion of cells with non-modal counts was 15%.* The distribution of the individual probabilities is shown in table III. From the table it appears that there is a tendency to record counts with the more extreme probabilities, but, with the present number of observations, we cannot be sure that this is not a chance finding (χ^2 = 11·66, n = 9, 0·2 < P < 0·3). The most extreme probability recorded was in case H115 (a man with idiopathic acquired hæmolytic anæmia), in this subject 8 of 29 cells counted showed 45 or less chromosomes and 3 cells showed 47 chromosomes. The probability of recording so many or more atypical cells is estimated at about 0·001. In our series of sixty-seven patients one probability of this order can be expected, by mere chance, slightly more often than once in 20 times (P = 0·06). It may be noted, however, that in this extreme case, the marrow preparation was regarded as technically poor before the count was made, and the whole preparation may well have contained more than the usual proportion of artefacts.

TABLE IV—CHROMOSOME COUNTS IN FOUR PERSONS WITH A MODAL NUMBER OF 45

Patient no.	Diagnosis	<43	43	44	45	46	47	>47	Total	Probability
H 98	Turner's syndrome	4	9	9	57				79	0·002
H138	,,	1	1		38		1		41	0·919
H153	,,	2			6	1			9	0·087
H188	,,			1	19				20	0·893
Total		7	10	10	120	1	1		149	

Difference between proportions of atypical cells, patients with modal number of (a) 46 and (b) 45

$\chi^2 = 2{\cdot}105$, n = 1, $0{\cdot}1 < P < 0{\cdot}2$

TABLE V—CHROMOSOME COUNTS IN THIRTEEN PERSONS WITH A MODAL NUMBER OF 47

Group	Patient no.	Diagnosis	<45	45	46	47	48	49	>49	Total	Probability
J	H114	Mongolism	1		2	35	3	1		42	0·367
	H119	,,				5				5	0·778
	H120	,,		1	4	22				27	0·295
	H121	,,	1		2	10		1		14	0·097
	H122	,,		1	2	33	1			37	0·748
	H124	,,			1	5				6	0·423
	H125	,,		1	1	31		2		35	0·705
	H127	,,	1	2	2	5	1			11	0·001
	H205	,,	2			16				18	0·648
Total			5	5	14	162	5	4		195	
K	H 54	Klinefelter's syndrome		1	5	20	2	1		29	0·141
	H100	,,	1	5	5	62	4			77	0·030
	H151	,,		1	1	12				14	0·498
Total			1	7	11	94	6	1		120	
L	H152	"Super-female"	1	1	4	49				55	0·795
Total all groups			7	13	29	305	11	5		370	

Difference between proportions of atypical cells, patients with modal number of (a) 46 and (b) 47

$\chi^2 = 1{\cdot}538$, n = 1, $0{\cdot}2 < P < 0{\cdot}3$

The data for patients whose cells show abnormal numbers of chromosomes are summarised in table IV (modal number 45) and in table V (modal number 47). In both the proportion of atypical cells is slightly greater than that recorded for subjects with a normal modal number of 46—i.e., 19·5% and 17·6% atypical counts compared with 15·0%. In neither is the difference significant, but the number of patients examined is still small and, if the expected proportion of non-modal counts was 15%, there were two patients (H 98 with Turner's syndrome, and H 127 with mongolism) with a type of count which would be expected to occur less often than once in 100 times. On the basis of these data, it seems wise to suspend judgment about whether the cells of patients with an abnormal karyotype may also show abnormal variability in the number of their chromosomes.

Discussion

In reporting the distribution of chromosome counts it has generally been accepted that the modal number represents the true somatic number, and that deviations from it are due to preparative faults. One may reasonably suppose, however, that mitotic errors occasionally occur in somatic tissues and give rise to cells with chromo-

TABLE III—PROBABILITY OF OBTAINING THE OBSERVED PROPORTION OF TYPICAL AND ATYPICAL CELLS: COMPARISON OF OBSERVED AND EXPECTED DISTRIBUTION (67 SUBJECTS WITH NORMAL KARYOTYPE)

No. of subjects	Probability										All probabilities
	<0·100	0·100–0·199	0·200–0·299	0·300–0·399	0·400–0·499	0·500–0·599	0·600–0·699	0·700–0·799	0·800–0·899	0·900 or more	
Observed	9	7	11	3	4	5	4	11	5	8	67
Expected	6·7	6·7	6·7	6·7	6·7	6·7	6·7	6·7	6·7	6·7	67

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* Since it was desired to examine the distribution of probabilities, the figure given is the probability of obtaining more than the observed number of non-modal cells plus half the probability of obtaining the number actually observed. This overcomes the difficulty resulting from the fact that the variable concerned is discontinuous. The mathematical justification for this technique is discussed by Lancaster (1949).

some numbers different from the modal number These errors are presumably due to non-disjunction, and are comparable to those that occur during parental gametogenesis In the latter case the affected gametes give rise to monosomic or trisomic individuals, so far represented in man by the clinical conditions of Turner's syndrome, Klinefelter's syndrome, mongolism, and the "superfemale" Ford and his colleagues have advanced the general argument that if a non-disjunctional error causes the loss of the Y chromosome in some of the cells of an XXY zygote, producing normal XX cells, and if normality offers some selective advantage over the cells with the abnormal trisomic condition, then a mosaic state could arise Mosaicism could also be the result of a non-disjunctional error at an early stage in the development of a normally constituted zygote, one of the resultant abnormal cells dying and the other persisting to give rise to a clone of cells with an abnormal chromosome number

There are, therefore, three possible reasons for the observed variation in marrow chromosome counts (1) artefacts, (2) mitotic abnormalities, and (3) mosaicism

In performing chromosome counts particular attention is paid to the cells in which the count differs from the modal number In our opinion the great majority of such cells arise during preparation, the most common fault being the rupture of the cell with the loss of one or more chromosomes Detailed study of the cells containing one chromosome more than the modal number reveals no evidence of an artefact, but there are reasons for thinking that the count is genuine in only a minority In the others the atypical count is due either to unrecognised splitting at the centromeres (the sister-chromatids being widely separated and enumerated as two chromosomes) or to the inclusion of a chromosome from a neighbouring cell If some of the cells with excess chromosomes are genuine there are also likely to be a few cells with true counts less than the modal number, though these cannot be distinguished from cells which have lost a chromosome or chromosomes through cell rupture The data from individuals with a normal karyotype (table I) show that less than 3% of cells have counts above the modal number Even if all these represented genuine aberrations from the modal number (which is very unlikely) and there was an equal proportion of cells with a true count less than the modal number, it would still follow that the majority of atypical cells were artefacts

In view of the variability of the counts in normal individuals it is clearly difficult to prove that a particular count indicates a mosaic In our opinion three criteria need to be fulfilled before the diagnosis can be established

1 The number of cells with counts different from the modal number must be more than can reasonably be attributed to chance (As more subjects are examined, more extreme variations are certain to be observed due to chance alone)

2 The excess of atypical cells must be demonstrable in two or more separate bone-marrow examinations and preferably in two or more tissues A suitable technique has been evolved for the study of chromosomes in the culture of skin (Harnden 1959), but a negative result from skin culture may not contradict the findings from marrow cultures, as two cell lines may be freely mixed within the marrow but occupy topologically distinct areas of skin, or mosaicism may be confined to the bone-marrow and not involve other tissues

3 A detailed analysis of the chromosomes in cells containing more or less chromosomes than the modal number must provide evidence that a high proportion of such cells have the same karyotype—i e , that the additional or the missing chromosomes are the same ones in different cells

The proportion of atypical cells reported by Ford and his coworkers in four patients (one presumptive XX/XXY mosaic, and three presumptive XO/XX mosaics) is much higher than could reasonably be attributed to chance on the basis of our experience It is, however, unsatisfactory to use data compiled by one group to test the significance of data collected by others and, so far as our own data are concerned, there is no reason to postulate the occurrence of a mosaic among the first eighty-four subjects to be examined

Summary

The distribution of chromosome counts has been analysed from the bone-marrow preparations of sixty-seven people who have shown an apparently normal karytope

The distribution is negatively skewed around the modal number of 46, 85% of the cells showing a count of 46 and approximately 12% a count less than 46 Of the latter more than half showed a count of 45 chromosomes The reasons for this type of distribution are discussed

The chromosome counts in four people with a modal number of 45 and in thirteen with a modal number of 47 have also been studied While the number of such persons is small the indications are that no unusual distribution of counts occurs, although more data are required for a final conclusion

Certain criteria are suggested, which ought to be satisfied before a diagnosis of a chromosomal mosaic involving two or more cell lines can be substantiated

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CASUALTIES AND CASUALS

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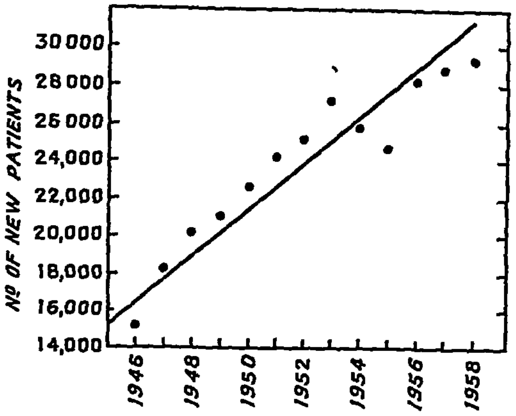
THOUGH within the bounds of the hospital, the casualty department is an entity of its own, usually staffed by junior doctors with a very brief term of service Papers have been written and suggestions made on how it should be planned (Clarkson 1956, Lowden 1956, Bowen 1957, Hilzinger and McAllister 1957, Shortcliffe 1958) but little is known about the character, incidence, and disposal of the cases seen in it The only previous analysis known to me was confined to medical patients (Mestitz 1957)

I record here my experience of 5000 attendances seen by me consecutively in the casualty department of a London teaching hospital, between July and December, 1958

The Department

The hospital is in south-east London, in a densely populated area Most of the people belong to the lower social classes, and there are about 25,000 Jamaicans in the neighbourhood

The department has a medical staff of five Two are post-registration appointments, and three are pre-regis-



Increase of new patients attending casualty department.

tration Two of the pre-registration housemen work also in other departments of the hospital The casualty officers are ultimately responsible to a consultant surgeon at the hospital

Patients can be admitted under the casualty officer for up to forty-eight hours (after which they must be referred to the appropriate department), or they can be referred direct to a consultant Referral from casualty to the outpatient department is by the usual method All fractures are seen next day in the casualty fracture clinic, which is the responsibility of the orthopædic department

The continuing increase in the number of new patients is shown in the figure

Reattendances in the department (at the doctor's request) tend to rise when a new set of casualty officers take up their posts, or when locums are employed Requests for reattendance also vary with the individual doctor In my personal series there were 2935 new patients (60%) and 2065 reattendances (40%)

The Series

The age-distribution of the 5000 patients is shown in table I

TABLE I—AGE-DISTRIBUTION

0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+
799	1060	985	765	641	342	178	230
16%	21%	20%	15%	13%	7%	3·5%	4·5%

There was a male preponderance of 3 to 1 (3680 males and 1320 females)

The sources of the new patients were

Casuals (patient comes on own initiative)	1825 (62·5%)
Referred by general practitioner	711 (24%)
Accidents	303 (10%)
Other emergencies	96 (3·5%)
Total	2935 (100%)

Thus nearly two-thirds of the new patients were "casuals", many of whom could have been dealt with by the family doctor *Mestitz (1957) in his series found that* 80% of the medical patients in the casualty department were casuals

A third (980) of the new patients were X-rayed, and 8% (170) had investigations (other than urine testing) on attending the department The majority of these were culture of pus from septic lesions

The diagnoses are shown in table II

The cases of *trauma* (51%) may be subdivided as follows

Minor trauma	1042 (71%)
Major trauma	22 (1·5%)
Fractures	272 (18%)
Head injuries	94 (6%)
Burns	56 (3·5%)
Total	1486 (100%)

Of the 286 cases of *sepsis* 119 (41%) required surgery

Of the 284 cases classified as *surgical*, 36 (12%) were acute —e g, acute abdomen Of the remaining 248—e g, orthopædic problems, patients with pain in the abdomen, or various swellings, sent to casualty for an opinion—only 57 (23%) required minor surgical procedures in the department

Of the 338 *medical* cases, 78 (23%) were regarded as acute —*e g, overdose of* barbiturates, coal-gas poisoning, cardiac infarction, hæmatemesis, epilepsy, or cerebrovascular accident. Another 50 (15%) *had* obviously psychiatric illness (not the minor neurosis from which a number of the patients were probably suffering)

The remaining 210 (62%), classified as non-acute, comprised a very wide range of conditions met with in everyday general practice, varying from peptic ulcer and longstanding cardiac failure to constipation, infections of the upper respiratory tract, and the exanthemata

Of the 115 *ophthalmic* cases, 90 (78%) were grouped as minor trauma and foreign bodies, while the other 25 (22%) were not casualty problems but outpatient problems

E N T—Of the 87 *ear, nose, and throat* cases, 68 (78%) were "medical" (the type of case common in general practice) these included tonsillitis, acute otitis media, and acute sinusitis The rest were "surgical"—i e, fishbones in the throat, *foreign bodies in the ears or nose, or epistaxis*

TABLE II—DIAGNOSTIC CLASSIFICATION

Trauma	Sepsis	Surgical	Medical	Eyes	E N T	Miscellaneous	Total
1486	286	284	338	115	87	339	2935
51%	10%	10%	11%	4%	3%	11%	100%

E.N T = ear, nose, throat

Finally, the *miscellaneous* group of 339 patients included 152 dental cases (5% of the total new attendances), 10 obstetric and gynæcological cases, 48 drunks, 8 cases certified dead on arrival, and 74 in which nothing abnormal could be found This leaves 47 unclassified, such as the woman who wanted her coffee analysed for an aphrodisiac, and a number of overseas visitors who had run out of their tablets, &c, while on holiday in England

Table III relates the main diagnostic groups (table II) to the source of the patient

A comparison of casuals with cases referred by practitioners shows considerable similarity In both groups half the cases were trauma, and about 10% were sepsis In the surgical group, however, there is a higher proportion of cases referred by practitioners Patients were often sent to the casualty officer for a second opinion (in many cases it was a "pre-registration" opinion), for minor surgical procedures, or as a bypass to the outpatient department Under the heading of "medical", the casuals have a much higher proportion of psychiatric cases than the referred patients, but the latter are a selected group in that many were sent to the casualty department as a means of avoiding waiting-lists, or for a second opinion That more of the "miscellaneous" group are casuals is due to the casuals including more dental cases

TABLE III—DIAGNOSTIC GROUPS RELATED TO SOURCE OF PATIENTS (%)

—	Trauma	Sepsis	Surgical	Medical	Eyes	E N T	Miscellaneous	Total
Casuals	50	10	8	10·5	6	3	12·5	100
Referred by general practitioner	48·5	12·5	19	10	1·5	2·5	6	100
Accidents	88		0·5	1	1		9·5	100
Emergencies			4	73			23	100
Total	51	10	10	11	4	3	11	100

TABLE IV—DISPOSAL OF NEW PATIENTS

—	Trauma	Sepsis	Surgical	Medical	Eyes	E.N T	Miscellaneous	Total
Reattend	500 (*33%*)	252 (*88%*)	91 (*32%*)	41 (*12%*)	76 (*67%*)	13 (*15%*)	7 (*2%*)	980 (*33%*)
Discharged	490 (*33%*)	10 (*4%*)	33 (*12%*)	95 (*29%*)	25 (*21%*)	28 (*32%*)	203 (*60%*)	884 (*30%*)
Referred to general practitioner	160 (*11%*)	23 (*8%*)	28 (*10%*)	55 (*16%*)	2 (*2%*)	33 (*38%*)	18 (*6%*)	319 (*11%*)
Admitted at once	128 (*9%*)		31 (*11%*)	77 (*23%*)			28 (*8%*)	264 (*9%*)
Referred to another department in the hospital	204 (*14%*)		98 (*34%*)	54 (*15%*)	12 (*10%*)	13 (*15%*)	61 (*18%*)	442 (*15%*)
Miscellaneous*	4	1	3 (*1%*)	16 (*5%*)			22 (*6%*)	46 (*2%*)
Total	1456 (*100%*)	286 (*100%*)	284 (*100%*)	338 (*100%*)	115 (*100%*)	87 (*100%*)	339 (*100%*)	2935 (*100%*)

*e.g , referred to duly authorised officer, self discharges

Of the emergencies—i e , those brought by ambulance —73% were medical, and of these nearly a quarter were classified as psychiatric (This does not include the large proportion of attempted suicides which were classified as acute medical) It is also noteworthy that 4 patients of the accident group were classified as psychiatric They had attempted suicide by physical means but were found to have no physical injuries

Table IV shows the disposal of the patients

Of the casuals, about half were discharged from hospital treatment (table V), 15% were definitely hospital problems, being either admitted or referred to another department, and 35% were retained under the care of the casualty department Of the patients referred by practitioners, 25% were sent back to their doctor, 25% had eventually to be referred to another hospital department, and 9% required admission, although the casualty officer was not responsible for admitting practitioners' patients

TABLE V—DISPOSAL RELATED TO SOURCE OF PATIENTS (%)

—	Re-attend	Dis-charged	Re-ferred to G.P	Re-ferred to other dept	Ad-mitted	Miscel-laneous	Total
Casual	35	39 5	9	12 5	3	1	100
Referred by general practitioner	27 5	13	25	25	9	0 5	100
Accident	30	18 5	3	9	36 5	3	100
Emergency	1	33	5	7	41	13	100

40% of the accidents and emergencies were admitted On the other hand 17 5% of accidents and 33% of emergencies were discharged on their first visit, although all had arrived in ambulances Mestitz (1957) thought that, of 52 medical patients reaching casualty by ambulance, only 29 needed such transport

Table VI shows the average number of visits (first and subsequent combined) for each diagnostic group, and the number of reattendances for these groups

Taken together, tables IV and VI show that trauma, sepsis, and eye cases accounted for 84 5% of the reattendances, though they formed only 65% of the new cases These groups may be regarded as "specific" casualty problems Patients with "sepsis" paid more visits to the department than any other group The fact that the average number of attendances is 1 8 indicates that most patients are not retained under the department for any length of time

TABLE VI—NUMBER OF VISITS OF REATTENDERS AND AVERAGE NUMBER OF VISITS FOR A PATIENT ATTENDING THE DEPARTMENT

—	No of visits of reattenders	Average no of visits per patient
Trauma	1015 (*49%*)	1 5
Sepsis	572 (*28%*)	3 7
Surgical	190 (*9%*)	1·6
Medical	110 (*5%*)	1 3
Eyes	151 (*7 5%*)	2 3
Ear, nose throat	9 (*0 5%*)	1 1
Miscellaneous	18 (*1%*)	1·0
Total	2065 (*100%*)	1 8

There were two reasons for asking patients to come again Firstly, treatment begun in the department and regarded as "casualty treatment" is continued there The second reason was to check on a case The casualty officer is acutely aware of litigation against his section of the medical profession, and most pre-registration housemen lack the confidence, or clinical judgment, needed to discharge some of the patients who do not require further hospital treatment Reattendances in the department generally fall towards the end of the casualty officer's term of office, when he has acquired more confidence

Discussion

The word "casualty" implies an accident or a serious or fatal event, but present-day casualty work is certainly not confined to accidents Indeed it could literally be called "general practice", for every aspect of medicine is encountered This conforms to the pattern before the National Health Service when patients attended the hospital outpatient or casualty department for all manner of illnesses because they could not afford the doctor's bills With the advent of the N H S , casual attenders might have been expected to disappear from the hospital, but at King's College Hospital the number of new patients has nearly doubled in the past twelve years (see figure)

Present Status of Casualty Department

Agreement has not yet been reached on the part the casualty department should play Should it see all patients who present themselves or should some selection be enforced? In my own series only 60% of cases were "casualty" problems, and of these the majority were minor trauma

Nearly two-thirds of the attendances were by the casual attender Reasons for such visits were

1 Some patients had themselves decided that their problem was one for the hospital—either because they thought it urgent, or because they felt they needed special investigations or treatment.

2 A few patients said that their doctors "would only have sent them to hospital anyway, so they came themselves"

3 Some had tried to contact their doctor, but had failed

4 The casualty department was always open, and this suited them better than their doctor's surgery hours Also they thought they would have to wait less time in casualty than in their doctor's surgery (In this they were sometimes mistaken.)

5 Some were not on any practitioner's list, or were staying only temporarily in the area and thought they could not call on a doctor

6 A few were dissatisfied with their doctor and wanted a second opinion

7 A proportion were sent from work or school

Are these reasons adequate? I doubt if all of them are In this country everybody is now entitled to a family doctor who should be responsible for his health and welfare If both the hospital and the family doctor are available for the patient to choose between, the result is duplication of services and weakening of the doctor-patient relationship Who should decide whether he goes to the casualty department—the patient himself or his doctor? When he is sure that he will be sent on to the casualty department, the patient naturally wants to avoid an unnecessary visit to his doctor first But, apart from this, some people seem to prefer hospitals to general practitioners

Use of Casualty by Family Doctor

General practitioners referred cases for various reasons

1 Trauma, for an X-ray to exclude bony injury, for suture of lacerations, or for treatment of fractures The X-ray department is not directly accessible to practitioners

2 Septic cases and a proportion of the surgical cases are referred for minor surgery Of the septic conditions referred, two-thirds eventually had surgical treatment

3 Some patients were sent for a second opinion—either directly from the casualty officer or from the outpatient departments to which casualty gives indirect access

4 Some cases were sent for admission without previous inquiry on whether the hospital had a bed for the patient.

5 In a small but significant number of cases the patient was sent for social reasons An old lady of 94 arrived with the following note "Will you please admit this patient I can find nothing wrong with her except old age" And some acute "psychiatric" conditions were referred to the department, for "social" reasons

Of these groups the true "casualty" problems were the trauma patients for minor surgery and a small proportion of the cases sent for admission—e g, overdose of drugs These amounted to about 60% of the referred cases The other 40% were a misuse of the casualty department, for they could have been dealt with through other channels

Future of the Casualty Department

Function—To have duplication of medical services is both uneconomical and unnecessary Casualty, like any other service, should have a specific function, and in my view it should deal only with trauma, emergencies (acute medical or surgical cases, 2% in this series), and minor surgery

Design—Dependent upon function, the department should be composed of three units—one for trauma, one for minor surgery, and one for emergencies The trauma unit should have its own beds, and be responsible for inpatient and outpatient care in its specialty

Staffing—The casualty department should be under senior hospital medical staff, who would be responsible for supervising and training the junior casualty officer

Centralisation—Obviously such a casualty department would not be needed in every hospital A given area should have its casualty centre at one particular hospital, where it would be maintained and staffed for its special purpose Centres should be fewer but better at present many of the casualty departments in this country are staffed by the pre-registration house-physician or house-surgeon on duty—people with no casualty experience

The future casualty department should not cater for the casual attender He has his family doctor to consult if he needs medical advice

Summary

This paper analyses 5000 attendances at a south-east London casualty department The patients form a consecutive series seen by one casualty officer

2935 (60%) were new attendances, and nearly two-thirds of these were casual attenders not referred by a doctor Only half the new patients were classified as trauma

In this department the number of new patients has doubled over the past twelve years, though under the National Health Service all patients can go to their family doctor without expense

The present-day casualty department has no specific function and runs as a "general practice" It is misused to a considerable extent both by the public and by their doctors

Future casualty departments should have a specific role Meanwhile more work is necessary both to review existing casualty services and to define their proper function and location

I should like to thank Mr L T Cotton for permission to conduct this survey, and the casualty reception staff for their valuable cooperation My thanks are also due to Dr John Fry for his encouragement and criticism But the views I express are my own

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DOCTORS AND NATIONAL SERVICE

THE chairmen of the National Medical Manpower Committee and of the Central Medical Recruitment Committees have issued the following statement

"The announcement made by the Minister of Labour on Dec 14, 1959, that certain persons whose deferment for training or study ends on or after June 1, 1960, will not be called up does not apply to doctors or dentists Doctors liable for National Service have always been dealt with under special and separate arrangements through the three professional committees, which advise on deferments and call-up matters These special arrangements will continue until the end of 1960, when call-up is planned to end.

"Under these arrangements deferment granted for completion of studies is continued during the pre-registration year, during which all doctors receive a memorandum setting out the arrangements for call-up and for further deferment

"Doctors who become provisionally registered as medical practitioners on or after Jan. 1, 1960, and doctors granted deferment of call-up to a date beyond the end of 1960 need not, subject to fulfilment of their deferment conditions, expect to be called up except in emergency

"All other doctors will, if fit, be considered for call-up in the usual way They will accordingly be nominated for National Service commissions (two years), unless they volunteer to enter the Forces on short service or regular commissions, or unless their call-up is deferred by the Central Medical Recruitment Committees on professional grounds or postponed by the Ministry of Labour on grounds of exceptional hardship

"In 1960 the Forces will still have substantial requirements for medical officers, which will need to be met largely from doctors liable for National Service This means that a considerable number of such doctors must expect to be called up during 1960"

In England Now

A Running Commentary by Peripatetic Correspondents

READERS of the best spy stories have long realised that to qualify for the higher echelons of spying a man must be a polished cracksman, a fluent polyglot, and a perfect shot (knife and gun), he must know the odds and modes of cheating at all games of skill and chance, and (if he is a hero) he must also be an appreciative connoisseur of life, for otherwise the Game would hardly be worth the candle—especially as the candle is usually alight at both ends and will be applied to the soles of his feet sooner or later. Of course, if he is a villain, villainy alone is a sufficient motive.

In view of all this literary conditioning, it is doubtful whether there are many people in England who really believe that spies exist. Ours is a land of charming naïvete where evil is concerned—a land of amateurs. We are not accustomed to consider blackmail, perversion, and revenge as common reasons for adopting a profession so inconvenient as intrigue appears to be. We have built up a melodramatic picture of the spy, and, because in our watercolour country we have come to regard as mildly absurd whatever is vivid, we find the idea of the sinister spy either ridiculous or incredible. Probably we shall never be able to assess the evidence on which the accusation was made that a Communist diplomat set afoot the grotesque plan to poison most of the staff of Radio Free Europe by putting atropine in the saltcellars of the canteen. The idea is too fantastic, the English imagination boggles—and then is tempted into a shamefaced chuckle at the notion of several hundred people simultaneously stuffing themselves with deadly nightshade. As like as not, tasteless jokes about the tastelessness of institutional soup will soon become current in student circles, while dons will quote the *Mithridates* passage from Housman or exchange thin-lipped smiles when the cruet passes between the protagonists of some High Table feud.

With our flippant heritage, how can we fail to look on the Bad Man as an object of pity and of decently moderate derision? Anarchists, nihilists, world-dominators, men who hate women, women who hate men, Nazi fascists, inquisitors, Communist fanatics—we are sorry for them. Why do these people make themselves so wretched, we ask first, and then—why must they also try to make *us* wretched? Can it be that for them happiness is harder work than spying, cheating, lying, destroying, torturing? And if this is true for certain individuals, can it also be true for whole nations? And is extremism always destructive, or is there a cause into which it is right to throw all our energies without reservation? Only one suggests itself: the cause of sanity—in other words, of realism, compassion, humour, and truth. These are virtues which never start wars, although, if necessary, they will *wage* war, invincibly.

* * *

Little attention is usually paid to hospital fauna, but ours at least are interesting.

A pet tortoise survived the whole of the war and on its demise was buried outside the operating block. Its tombstone was inscribed with the touching lines

> "Chloe was a beautiful tortoise,
> Even in rigor mortis."

The other day I went into one of the anæsthetic rooms and found a robin perched on a gallipot pecking away at some K-Y jelly which was used to lubricate airways. As I believe that this substance contains glycerin and gelatin, I suppose that he found it sweet and with sound food value.

Last year our neurosurgeon had a surprise. At the end of a craniotomy he asked a nurse to puff his favourite penicillin-sulphanilamide powder into the wound. When she squeezed the bulb, however, a cloud of tiny Egyptian ants emerged. The resulting consternation was mitigated by the bacteriologist, who reported that they were not only sterile but strongly antiseptic. The suggestion that they should in future be sprayed into all wounds has not been followed up.

* * *

My elderly car has just returned to the road after a long illness patiently borne by both of us, and I have been quite touched by people's interest and solicitude.

I used to meet a rubicund man with a large dog every day, and we usually exchanged noncommittal looks, but he waved enthusiastically at my reappearance. A bored-looking woman who is always hanging over her cottage gate, whatever the weather, shouted a greeting. An elderly cyclist, by whose whereabouts on the road I could tell whether I was early or late, made the thumbs-up sign. The butcher in the village grinned and nodded encouragingly as we rattled past his shop. (He once gave me a lift in his van when he saw me panting along towards the hospital at a brisk trot.) And, of course, the porters at the hospital, who had evidently missed my noisy reversings and erratic startings outside their window, came out to admire and congratulate. Even the cows in the fields looked vaguely approving.

The only people who were not sympathetic were the stony-hearted bureaucrats who would not refund the cost of an entirely unused quarterly licence, which ironically enough I had for once renewed in good time.

* * *

She was wearing dark glasses and she said that as she was suffering from nervous debility she thought she would go on the club for a bit. Hoping for a more accurate diagnosis, and to ease my conscience before issuing the inevitable N.I. certificate, I incautiously asked her what she meant by nervous debility. I suppose I deserved her answer: "Well, you're the doctor." I explained that the expression sometimes meant that people were overtired or worried and that it would help me to put things right if she would tell me a little more. "Well, as a matter of fact I've had a blow," she said. "Do you mean the sort of blow you would feel from the loss of a relative, or have you been hit by something?" I inquired. "I've been given a blow by a relative," she replied, and there, as she removed her glasses, was a fine black eye. "You haven't got nervous debility," I said firmly, as I scribbled the Form Med. 1, "you have got a periorbital hæmatoma." I felt better about it that way.

* * *

Thoughts on the N.H.S. while reading to my children

"Please pass the buck," the Walrus said
And shed a bitter tear.
"You'd think they should have settled this.
Instead, they've sent it here.
It's travelled round from him to them
And back again to me
From Records to the Ministry
And to the R.H.B.
Initialled *here* by Tweedledum
And *here* by Tweedledee.

"Please pass the buck," the Walrus said.
"A subcommittee call
And make it large and wide enough
To subcommit us all.
In case the matter's surgical
The Carpenter shall speak
And every Hatter madly grin
And every Dormouse squeak.
With any luck the meeting will
Go on for half the week."

"Please pass the buck," the Walrus said.
"My conscience must be free.
My pidgin isn't medical,
Admin's my cup of tea.
The Service bids us trim our sails
To all the winds that blow.
Committees are deliberate—
Who dares to call them slow?
For twenty men will say "perhaps"
When any one says "no."

Letters to the Editor

A CENTRAL LABORATORY FOR OCCASIONAL INVESTIGATIONS

SIR,—Dr Hughes-Davies (Jan 2) raises the question of how the general physician could gain access to specialised laboratory services, and suggests a national biochemical reference laboratory, on the lines of the bacteriological reference laboratories

The problem, however, is not quite the same as in bacteriology, either in the pattern of work of such a central laboratory or in the numbers of specimens likely to be submitted, and to establish a worthwhile central laboratory for clinical biochemistry presents formidable problems Few physicians have any idea of the amount of work which can result from a request which may take only a few seconds to write, and not all physicians would restrict their calls on such a laboratory to the occasions where its help is really necessary If, for example, the laboratory were to offer to measure urinary catechol-amine excretion, many physicians might come to regard this analysis as part of the routine investigation of hypertension From the patient's point of view this may be justified, however long the odds may be against finding a significantly increased excretion, but the effect of such requests, on a national scale, would be to make the central laboratory quite unworkable It is also possible to visualise, in advance, the flood of M D theses, both good and bad, which could arise from the work of such a laboratory if it attempted to meet all calls made on it

A more practicable arrangement might be for each of the larger laboratories in a region to make itself responsible for two or three of the more technically exacting analyses, and for requests to be passed on to these laboratories through local biochemists or clinical pathologists Unofficial arrangements of this sort already exist in many areas, but to put such arrangements on a more general footing should not be unduly difficult It is, I think, very desirable that such arrangements should be of a strictly regional character, since otherwise it is hardly practicable for the request to be discussed between the biochemist and the physician concerned, and it is also desirable that physicians should understand the right of the senior laboratory worker to query, and on occasions defer or reject, a request which may take him many hours of work to meet and of whose necessity he is not convinced Work of this character is not performed by junior technicians, and it is necessary for the man at the bench to be reasonably satisfied that his efforts are not being wasted

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S C FRAZER

SIR,—On the face of it, Dr Hughes-Davies' suggestion that the National Health Service should establish a central laboratory able to make certain tests on a routine basis appears to be quite good It does, however, overlook the fact that there are now a large number of group or area laboratories in the National Health Service which are already undertaking most of the tests he has mentioned There may be some difficulty about hormone investigations requiring maintenance of large stocks of animals, but many biochemical estimations, sometimes regarded as infrequently required, are now routine tests in the larger laboratories Moreover, many group laboratories have an interchange system whereby a laboratory can supplement its own battery of tests by referring special work not usually done by it to another group laboratory

The suggestion made by Dr Hughes-Davies also does not take account of the fact that the most important part of a test is interpretation of the result in relation to the patient, expert guidance of this kind is not always easy to obtain from a central laboratory which gives only a postal service

The Mental Hospitals'
Group Laboratory, at
West Park Hospital,
Epsom, Surrey

W W KAY

CHROMOSOME STUDIES IN LEUKÆMIA

SIR,—In their letter of Oct 31, Dr Ford and Dr Mole make one interesting and justifiable comment on the interpretation of our observations in relation to the occurrence of chromosomal abnormalities in human leukæmia We would agree that it is possible that the absence of chromosome abnormalities in our cultures of marrow from patients with one or other type of chronic leukæmia is due to the leukæmic cells not having divided in culture This being so, the cells of an apparently normal chromosome constitution which we observed would be derived from normal marrow elements It is now possible, however, to test if any unusual numbers of cells were present in these cultures with chromosome counts differing from the modal number by calculating the expected numbers of cells with typical and atypical (non-modal) counts and comparing these numbers with the observed numbers [1] If a small but significant excess of atypical cells were present there would be some justification for believing that we were observing some abnormal leukæmic cells but, because of their small number, classifying them as artefacts We have now made such calculations for 8 cases of chronic leukæmia (5 of chronic myeloid and 3 of chronic lymphatic) inclusive of the cases reported in our paper (table I) From these calculations it can be seen that there is no difference between the expected and observed numbers of non-modal cells in the marrows from patients with chronic lymphatic leukæmia In those from patients with chronic myeloid leukæmia there is a small excess of atypical cells but this may well be due to the play of chance ($\chi^2 = 2\ 40$, P > 0 1)

We feel, therefore, that, if the cells of chronic leukæmia carry a chromosomal abnormality, the abnormality may be of such fineness as to be below the visual threshold of our technique We cannot exclude, however, the possibility that visible abnormalities may occur but remain hidden from us because either the culture times are too short or the conditions of culture are harmful to these types of cell

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A G BAIKIE
W M COURT BROWN
PATRICIA A JACOBS

WHAT TO EXPECT FROM OUR BABIES

SIR,—The reader of your annotation of Jan 2, dealing with a recent special report of the Medical Research Council, might legitimately conclude, if he had not had the opportunity of studying this interesting report, that the author's claim to have established weight standards for the first year of life, according to birthweight, based on examinations of over 700 infants

Although reasons are given in the report for assuming that the 15% of cases remaining in the sample at the age of 8–12 months is representative of the sample as a whole, it would not seem reasonable to accept as standards mean weights based, for example, at 5–6 months on 5 cases in the 2–3 lb birthweight group, 8 in the 3–4 lb, and 23 in the 4–5 lb groups Nor can it be said that the findings in this report isprove the supposition that many infants smaller at birth emain at the lower end of the normal weight scale

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[1] Court Brown, W M, Jacobs, P A, Doll, R *Lancet*, Jan 16 1960, p 160

Current studies in Edinburgh indicate that the prematurely orn tend to remain smaller than average in the preschool eriod, and though this can be attributed in part to less avourable environment and small parental stature, many of hose in the 2–3 lb birthweight group remain markedly ndersized well into the school-age period, even when there s no obvious effect of environmental or genetic factors In hese cases at least "the accident of gestational age" appears o have a marked effect on the "inborn pattern of body size"

Department of Child Life and Health,
University of Edinburgh
C M DRILLIEN

MEDICAL JOURNALS FOR DOCTORS IN DEVELOPING COUNTRIES

SIR,—Your account (Jan 2) of the scheme which is being started to enable British doctors to send their medical journals on to colleagues oversea is doubly gratifying,' first, because of the excellent project that you describe, secondly, because you refer to *developing* countries and only permit "underdeveloped" to appear between quotation marks It has become customary to refer to "underdeveloped countries", but this is scarcely a satisfactory designation There are many underdeveloped countries, such as Australia, which are not being referred to, and the phrase has a rather unpleasantly patronising flavour I therefore hope that others will follow your example, and that "underdeveloped" will no longer be used to designate newly developing countries

St Paul s Cray,
Orpington,
Kent
L M FRANKLIN

THE COST OF DRUG TREATMENT

SIR,—The article in your issue of Jan 2 by Dr Miller and Dr Smith is full of most useful information and, in general, appears to be an objective report on a problem which has, in many other quarters and on many occasions, been treated in anything but an objective manner There are, however, features of the article to which I feel that further attention should be drawn, particularly as those features have led to quotation (or misquotation) in the *Daily Express*

The feature to which, from the pharmaceutical standpoint, the greatest exception is taken is the quoting of the "basic cost" per week of phenobarbitone therapy and the development from it of the contention that the chemist-contractors' remuneration increases the cost by more than 1600% If I were to contend that on each patient whom a medical practitioner has on his list and who requires no attendance or other service during the year, the medical practitioner makes an astronomical *percentage* profit I would be just as accurate but just as unfair as Dr Miller and Dr Smith

They also draw attention to the fact that in their calculations a flat-rate dispensing fee of 1*s* 2*d* has been added to the basic cost "but that in fact this is the minimum" By quoting one higher fee of 4*s* 0*d* they imply that the minimum fee is not the fee usually met with In fact, the national average dispensing fee, assessed over 200,000,000 prescriptions, is 1*s* 2 8*d*, and it should be noted that that level of remuneration was only conceded by the Ministry of Health after the most exhaustive costing investigations and subsequent "negotiations" in which figures to the fourth place of decimals featured prominently and in which all increases in salaries and overhead costs which have occurred since 1956 were completely disregarded

As to the contention of Dr Miller and Dr Smith that because "rather more than three-quarters of all National Health Service prescriptions are for tablets" their "dispensing does not call for any high degree of professional skill", they are, in my view, adequately and best answered by the fact that (as the Minister of Health has, himself, said) "the role of the pharmacist is vital in the handling of these products" and has led to an increase in the severity of the educational standards required for entry into and subsequent qualification in the pharmaceutical profession

H NOBLE
Secretary, Central N.H S
(Chemist-Contractors) Committee
London, W C 1

THROMBOTIC THROMBOCYTOPENIC PURPURA

SIR,—Dr Bernstock and Dr Hirson's paper of Jan 2 quotes several examples from the literature Presumably because the paper was written before our case was published[1] they have not had an opportunity to comment on that This might be an opportunity to point out that our child, who was $2^1/_2$ years of age at the onset of the disease, completely recovered, following a five-week course of cortisone There was no clinical or hæmatological relapse subsequently, and to date, two years after his admission, he is a perfectly normal little boy

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J LORBER

PROPHYLAXIS IN THROMBOEMBOLISM

SIR,—In a leading article on Dec 5 you stated "What little theoretical understanding we do have is still based on the triad of causes enunciated with extraordinary vigour and lucidity by Virchow " It is probably that because it was said with vigour by a master we cling to this concept and give little attention to other probable explanations

It can be stated with considerable assurance that two of the factors of the triad—namely, altered coagulability of the blood and impaired circulation—are rarely, if ever, primary in the causation of intravascular clotting In fact, it is still a moot question whether hypercoagulability has ever been unequivocally demonstrated Progress in understanding thrombosis and abnormal bleeding has been hampered perhaps more by the myth that the clotting-time is a measure of physiological coagulability than by any other theory of coagulation

Coagulability implies formation of thrombin, and the defence against massive intravascular clotting is the prompt removal of this clotting factor from the circulating blood In a recent study, my associates and I[2] have reconfirmed the observation that when thrombin is injected intravenously at a slow steady rate, it does not cause thrombosis We offer the explanation that thrombin is promptly removed by adsorption to the surface of fibrin fibrils which are rapidly removed from the circulating blood

The thrombin that gives rise to a pulmonary embolus is generally regarded as having its origin in the peripheral venous system It has been postulated[3] that it may be initiated by a localised injury of a vessel wall Such an injury liberates enough tissue thromboplastin to cause the formation of the primary clot attached to a vessel wall When this clot retracts, it expresses a serum rich in nascent thrombin If this serum is not promptly swept into the circulation, a secondary clot attached to the primary thrombus is produced By a multiple repetition of this process, the thrombus grows in the direction of the blood-stream and when dislodged from its mooring becomes a pulmonary embolus

The success of anticoagulant therapy, as again convincingly demonstrated by the excellent paper of Sevitt and Gallagher,[4] can be explained satisfactorily by the above theory The prompt neutralisation of thrombin by heparin or the depression of the thrombinogenic activity of the blood by a drug decreasing prothrombin activity effectively prevents the growth of the thrombus because the clotting activity of the expressed serum is greatly reduced by either agent.

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[1] Lorber, J , Emery, J L *Proc roy Soc Med* 1959, 52 301
[2] Quick A J , Hussey, C V , Harris, J , Peters, K *Amer J Physiol* 1959, 197 791
[3] Quick A J *Practitioner* 1951, 166 213
[4] Sevitt, S , Gallagher, N G *Lancet*, 1959 ii, 981

Marquette University,
Milwaukee, Wisconsin
ARMAND J QUICK

THE NATURE OF ESSENTIAL HYPERTENSION

SIR,—In your review (Jan 2) of *Medical Surveys and Clinical Trials*, edited by L J Witts, you say " Once again the professional habit of dividing normal from abnormal systolic blood-pressure at about 160 mm Hg appears to be reasonable " I would be greatly obliged if you or any of your readers would furnish me with the evidence on which this statement is based

Oxford
G W PICKERING

*** The evidence was discussed in our leading article of Nov 21 and the letters we have since printed Sir George interprets our review as suggesting that the issue is settled —which would certainly be going too far The customary division between normal and abnormal pressures was described only as " reasonable " —ED L

CASE-FATALITY IN TEACHING AND NON-TEACHING HOSPITALS

SIR,—In 1957 we showed [1] that there was a higher case-fatality for certain conditions in non-teaching hospitals than in teaching hospitals This study was based on the data collected by the General Register Office in the national Hospital Inpatient Morbidity Enquiry for England and Wales in 1951 and in 1953–54 The collection of data has continued, and that for 1955 has recently been published [2] [3] We have tried to analyse this new material, together with some additional unpublished data supplied by the General Register Office and the Ministry of Health, in the same way as the earlier

TABLE I—NUMBER OF CASES OF HYPERPLASIA OF PROSTATE, NUMBER OF DEATHS AND CASE-FATALITIES IN TEACHING AND NON-TEACHING HOSPITALS, 1953–54 AND 1955 (MEN AGED 45 YEARS AND OVER)

—	1953–4		1955	
	Teaching *hospitals*	Non-teaching *hospitals*	Teaching *hospitals*	Non-teaching *hospitals*
Cases	290	729	112	671
Deaths	12	70	4	101
Case-fatality	4 1%	9 6%	3 6%	15 1%
Case-fatality standardised for age and mode of admission*	4 1%	7 8%	3 6%	11 3%
	(P<0·05)		(P<0·05)	

* Using the age structure, and the proportion of " immediate " admissions, of the teaching hospital cases in each period as the " standard " population

As time passes, the General Register Office and the Ministry of Health are able to make the Hospital Inpatient Morbidity Enquiry more representative The 1955 material includes effectively random samples of the patients discharged from very large numbers of non-teaching hospitals, including those of two complete regions, and from nearly half the teaching hospitals in England and Wales However, the use of the same sampling fraction (10%) for both teaching and non-teaching hospitals means that in many conditions the number of cases and deaths reported by the teaching hospitals is very small Because of this the data for appendicitis and for diabetic coma, for both of which there was a marked difference in the experience of teaching and non-teaching hospitals in the earlier study, cannot usefully be analysed for 1955 But there were enough cases and deaths from hyperplasia of the prostate and from perforated peptic ulcer in the 1955 material for analysis in some detail

TABLE II—NUMBER OF CASES OF PERFORATED PEPTIC ULCER, NUMBER OF DEATHS AND CASE-FATALITIES IN TEACHING AND NON TEACHING HOSPITALS, 1953–54 AND 1955 (MEN OF ALL AGES)

—	1953–4		1955	
	Teaching hospitals	Non-teaching hospitals	Teaching hospitals	Non-teaching hospitals
Cases	144	280	52	240
Deaths	12	33	9	31
Case-fatality	8 3%	11 8%	17 3%	12·9%
Case-fatality standardised for age*	8 3%	9 8%	17 3%	10·6%
	(P>0 05)		(P>0·05)	

* Using the age structure of the teaching hospital cases in each period as the ' standard ' population

Hyperplasia of the Prostate

Case-fatalities in the two types of hospital in 1955 are shown with those of 1953–54 for comparison, in table I There is a significantly lower case-fatality among the teaching-hospital patients (3 6% compared to 15 1%) The different age-distribution of patients in the two types of hospital, and the different proportions of " immediate " or emergency admissions to them have made little contribution to this difference in case-fatality as is shown by its persistence (3 6% and 11 3%) when these factors are allowed for by simple standardisation

Some cases admitted to hospital with *retention of urine* were given no more specific diagnosis, they will certainly have included men with hyperplasia of the prostate For the period 1953–55, there were 49 such male cases aged over 45 reported by teaching hospitals, and 304 by non-teaching hospitals The case-fatality among these patients, when standardised for age and mode of admission in the same way as the cases definitely described as suffering from hyperplasia of the prostate, was 4 1% in the teaching hospitals and 15 0% in the non-teaching hospitals The relatively greater use of this less precise diagnosis by non-teaching hospitals cannot therefore have produced the observed difference in case-fatality in hyperplasia of the prostate

The death rate from hyperplasia of the prostate in England and Wales as a whole fell by 27% between 1951 and 1957 [4] There are no data on case-fatality later than 1955, but clearly the analysis of the 1956 and 1957 results of the Inpatient Morbidity Enquiry will be very interesting

Perforated Peptic Ulcer

In 1951–54 case-fatality from perforated peptic ulcer was somewhat higher in the non-teaching hospitals This difference was small and it was less regular than for hyperplasia of the prostate

There were just sufficient numbers of cases and deaths from this condition reported in 1955 for separate analysis The

TABLE III—NUMBER OF SURGEONS PER 1000 SURGICAL BEDS, IN TEACHING AND NON-TEACHING HOSPITALS, NATIONAL HEALTH SERVICE, ENGLAND AND WALES, 1958

Staff	Teaching hospitals	Non teaching hospitals
Consultants	26	17
Senior hospital medical officers	0 3	1 8
Senior registrars	18	2 2
Registrars, junior hospital medical officers	29	22

This table includes all surgeons appointed in general surgery, traumatic and orthopædic surgery, urology, plastic surgery, thoracic surgery, and neurosurgery, and all staffed beds in these specialities

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[1] Lee, J A H , Morrison, S L , Morris, J N *Lancet*, 1957, ii, 785
[2] General Register Office (1959) Statistical Review of England and Wales, 1955, *Supplement on Hospital Inpatient Statistics* H M Stationery Office
[3] *Lancet*, 1959, ii, 416
[4] General Register Office Unpublished

BLE IV—NUMBER OF ANÆSTHETISTS PER 1000 SURGICAL BEDS IN TEACHING AND NON-TEACHING HOSPITALS, NATIONAL HEALTH SERVICE, ENGLAND AND WALES, 1958

Staff	Teaching hospitals	Non-teaching hospitals
onsultants	18	10
enior hospital medical officers	0 7	2 7
enior registrars	5 8	0 6
egistrars, junior hospital medical officers	20	8 9

Surgeons and anæsthetists employed part-time in any of the above grades ave been converted to a whole-time equivalent on the basis of 38¹/₂ hours er week.

esult of this is given in table II The advantage in 1955 lay ith the *non-teaching* hospitals Such a reversal suggests that here is no real difference between the case-fatalities from erforated peptic ulcer in the two types of hospital

taffs of the Two Types of Hospital

In our earlier paper we commented on the substantial ifferences in the staffing ratios of teaching and non-teaching ospitals Figures for 1958–59 have kindly been made available to us by the Statistical Division of the Ministry of Health tables III, IV, and V) There has been little change since 1953 ata on numbers of house-officers in the two kinds of hospital re not available for 1958 No regional analysis has yet been ttempted

haracteristics of Patients

The point was made in correspondence[5] on our original aper that the social class of patients may affect their prognosis o an important extent, and that the distribution of patients by ocial class was likely to be different in the two types of hospital Unfortunately, the General Register Office were unable to btain the current, or most recent, occupation (whence "social class" is derived) from hospitals in 1951–55 for more than a small proportion of the patients We hope to be able to study this question later as a renewed attempt is being made to collect data on occupations

TABLE V—NUMBER OF NURSES PER 100 BEDS IN TEACHING AND NON-TEACHING "ACUTE" AND "MAINLY ACUTE" GENERAL HOSPITALS, NATIONAL HEALTH SERVICE, ENGLAND AND WALES, 1959

Full-time		Part-time	
Teaching hospitals	Non-teaching hospitals	Teaching hospitals	Non-teaching hospitals
84	49	3	12

No data are available on the distribution by surgical or medical beds, or on the whole-time equivalent of part-time nursing staff.

We are also making a more detailed study, in collaboration with one regional hospital board and board of governors, of their patients with hyperplasia of the prostate Information about the occupations will be available. An attempt is also being made to classify patients by their clinical condition before operation, and to analyse postoperative morbidity as well as mortality in the two types of hospital

Beds for the Chronically Ill

The possibility is sometimes raised that the presence of beds for the chronically ill in the non-teaching hospitals may increase their case-fatalities for such conditions as hyperplasia of the prostate,[6] and that these may also influence the staffing ratios and make their interpretation difficult. The data in the Hospital Inpatient Enquiry are based on the patient's total duration of stay, without regard to transfers *within* the hospital The number of long-stay patients in the non-teaching hospitals discharged or dying with a diagnosis of hyperplasia of the prostate cannot be large, for the durations of stay with this diagnosis are similar in the two types of hospital Moreover, it has already been shown that the extra mortality in the non-teaching hospitals could not be accounted for by such long-stay patients as they did have[1] The ratios of surgeons and anæsthetists are of course calculated per 1000 *surgical* beds, and are unaffected by the presence or absence of other types of accommodation, such as beds for the chronically ill, in the hospital The ratio of nurses to beds (table V) is in fact closely similar in non-teaching hospitals whether they are altogether "acute" or "mainly acute"

We are grateful to the General Register Office and the Statistical Division of the Ministry of Health for their help

J A H LEE
S L MORRISON
J N MORRIS

Social Medicine Research Unit
of the Medical Research Council,
London Hospital, E 1

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[5] Platt, R *Lancet*, 1957, ii 893

[6] General Register Office Statistical Review of England and Wales 1955 Supplement on Hospital Inpatient Statistics p 21 H M Stationery Office, 1959

THE CONVALESCENT EXCRETER OF SALMONELLÆ

SIR,—Dr Schrire (Jan 2) is unduly optimistic when he reports that few patients continue to carry *Salmonella typhimurium* or other intestinal pathogens after treatment In my experience the antibiotics so far available seem to have little effect on the salmonella carrier, nor does furazolidone fare better At Coppetts Wood Hospital 11 patients suffering from salmonella food-poisoning were treated with antibiotics (tetracycline, chloramphenicol, or streptomycin) and at the end of the course 9 continued to excrete the organism A further 7 patients were treated with furazolidone but with no greater success, for all became convalescent carriers The results of treating 8 cases of Sonne dysentery with furazolidone were equally disappointing, for in each case we obtained positive stool-cultures on completing treatment With such uniformly poor results furazolidone would appear to be of little value in treating the human salmonella carrier or the carrier of *Shigella sonnei*

Coppetts Wood Hospital,
Muswell Hill, London, N 10

RONALD T D EMOND

THE ABNORMAL APPENDIX

SIR,—In his helpful and readable article of Dec 26, Mr Jewers reiterates the feasibility and importance of early diagnosis and removal of the acutely inflamed appendix This general diagnosis covers a variety of clinical pictures, each dependent on the position of the inflamed organ and with its own particular differential diagnosis

While one cannot quarrel with Mr Jewers' paramedian incision, I suggest that easy and adequate approach can equally be by appropriate incision over the inflamed organ high muscle split in the flank for retro- or para-cæcal, transverse pararectal with lateral muscle-split extension and preservation of intercostal nerve and inferior epigastric blood-vessels for tethered retromesenteric and iliac, and lower midline for pelvic, or where peritonitis has developed Diffuse peritonitis is treated by early placement of damp mops, changed at intervals during the operation until they come out apparently clean, and the abdomen is closed without drainage

Transperitoneal drainage with a red-rubber tube of a localised inflammatory mass may be likened to the gastroscopic investigation of a wasps' nest on a drowsy summer afternoon, and may be the cause of fæcal fistula and adhesions

Acute intestinal obstruction, either of the small gut or of the appendix by a stercolith, is not amenable to conservative treatment The tethered retromesenteric inflamed appendix in particular must be removed early in order to forestall retromesenteric peritonitis, lower small-gut obstruction, and portal pyæmia

Mr Jewers' paper and his references are worthy of study

Royal East Sussex Hospital,
Hastings, Sussex

J A KERR

EARLY DIAGNOSIS OF PREGNANCY

Sir,—I was very interested to read Dr Foster's letter[1] on the early diagnosis of pregnancy using 'Disecron' and in Dr Hobson's doubts[2]

I should like to mention a test for the early diagnosis of pregnancy which I described in 1954 At that time, we first examined the cervical mucus to find out whether crystallisation "like fern leaves" took place, but we have now modified the method and give straight away 2 mg of œstradiol benzoate and 50 mg of progesterone together intramuscularly

We have used the method in more than 350 cases of delayed menstruation, and results have been excellent Two to eight days after the injection in all cases of non-pregnancy menstruation appears, and in all pregnancies no menstruation follows

Dr Hobson objects to the injection of steroid material because "we cannot be certain that the resulting hormonal imbalance, however small, may not itself cause an abortion in susceptible women" But, in my experience, exactly the opposite happens The steroids seem to have a beneficial effect on the fertilised ovum in women of low fertility by modifying the endometrium favourably

After more than 350 tests, the accuracy of the method using 2 mg of œstradiol benzoate and 50 mg of progesterone is better than the Aschheim-Zondek test (especially when frogs are used) The test is reliable, economical, and practical

Toronto L G Polymenakos

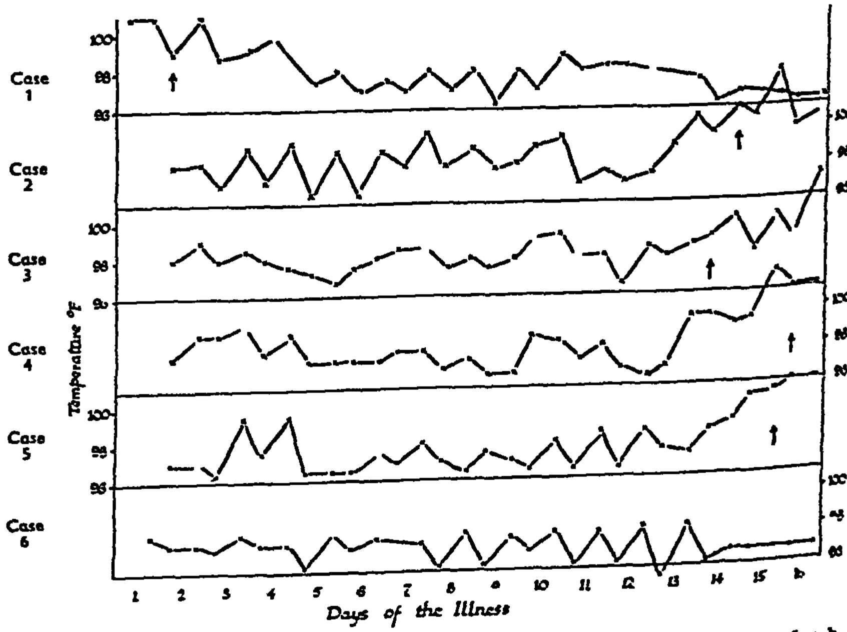
AN ILLNESS OF INFECTION IN CHICKENPOX

Sir,—An "illness of infection" was first recognised in measles by Goodall[3] in 1925 He described 4 patients who had a transient febrile illness within a day or two of exposure to measles This was followed by a period of apparently normal health before the usual prodromal symptoms and measles rash appeared Since that time over 30 cases have been reported in the literature It is estimated that about 10% of patients with measles have an illness of infection It has also been recognised that a small proportion of patients have symptoms throughout the incubation period[4]

It is quite possible that similar phenomena occur in other infectious diseases but the symptoms or clinical features are so mild that they escape notice Recently an opportunity arose to test this in chickenpox

One day the eldest boy (aged 11) of a family developed malaise, generalised aches and pains, and fever Next day he had a characteristic chickenpox rash Twice-daily oral temperatures were taken from all members of the family for the next 15 days No attempt was made to isolate the child

The temperature records are shown in the accompanying figure The first record is that of case 1, the boy already described. Case 6, the father, had previously had chickenpox, and his temperature stayed below 98 6 F for the whole of the observation period. All the rest of the family had typical chickenpox in due course. Case 5, the mother, had a temperature of 99 6°F in the evenings of the third and fourth days of case 1's illness During the same period the other 3 children had at least one temperature recording of 99 F, and case 4 had a reading of 99 6°F None of them complained of symptoms Thereafter the temperatures of cases 3, 4, and 5 remained below 99°F until the fever began before the rash appeared.



Temperature records of family exposed to chickenpox Arrows indicate appearance of rash.

Case 2, a girl of 7 years, showed a slightly different pattern. She had a temperature of 99°F or over on the third, fourth, seventh, and tenth days of the incubation period before prodromal fever developed.

These observations are clearly no more than preliminary and suggestive Their interest, if confirmed, is at least threefold First, it may be possible to identify a few more of the many unexplained fevers Second, when known exposure has occurred, it may be possible to predict that a particular person will develop the disease (the converse is not true) Lastly, these small rises of temperature provide some clinical support for the pathogenesis of the acute specific fevers outlined by Fenner[5]

Fenner suggested that first there is a local invasion of the body by the virus This is followed by a viræmia The virus then settles in the viscera, probably in the reticuloendothelial system It multiplies here during the incubation period and then issues forth in a further viræmia or series of viræmias. These, together with peripheral invasion of the skin, respiratory tract, &c. are responsible for the customary clinical features of the disease In this view the illness of infection represents the first viræmia or systemic spread of the organism

Fenner's theory was based on laboratory work with mousepox. Clinically, the onset of measles is consistent with his hypothesis The present findings suggest that a similar train of events could well occur in chickenpox

It should be possible to confirm or refute these observations by taking the temperatures of all exposed persons during an outbreak of chickenpox in other families, hospitals, nurseries, or schools

I wish to thank Mr T Foster of the Royal Infirmary, Sheffield, for the figure, and my family for being such patient guineapigs

Toronto M W Partington

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[1] *Lancet*, 1959, ii, 242
[2] *ibid* p 409
[3] Goodall, E W *Clin J* 1925, 54 69
[4] Partington, M W, Quinton J F P *Arch Dis Childh* 1959, 34, 149
[5] Fenner, F *Lancet*, 1948, ii, 915

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—Mr Azie (Dec 12) is to be congratulated on his successful treatment of a formidable case of ruptured ectopic pregnancy in difficult circumstances, and for advocating the method of autotransfusion which is so much neglected in this country nowadays

It is surely the ideal method of transfusion—the blood is perfectly compatible, it has been kept at body-temperature, it is to some extent defibrinated, it needs little or no anticoagulant, and, as Dr Burrowes (Dec. 26) has told us, it is acceptable to a Jehovah Witness The modern generation in this country has lost sight of the method, or more probably has never known it one recalls the story of the evacuee child at the beginning of the late war who said after seeing a cow milked that at home they didn't get milk like that but out of a nice clean bottle The increasing use of suction in theatres also perhaps tends to discourage it.

I have found that the easiest way to collect the blood is to have a borrowed soup ladle sterilised with the instruments, but the main difficulty nowadays is to find a suitable container to put the blood in While perhaps the method is indicated only in the fulminating sort of case described by Mr Azie and Professor Chassar Moir (Jan. 2) with a massive hæmorrhage, it would be unfortunate if the method were to fall into disuse in this country, and it is time we realised that we cannot always expect to live in a perpetual lotus-land, with, among other things, endless supplies of preserved blood easily available

Middlesbrough BRYAN WILLIAMS

SIR,—Mr Azie's letter reminded me of the early post-war years when blood-transfusion facilities were very poor even in large surgical centres in Greece At that time it was the rule to try to retransfuse as much of the intra-abdominal blood as possible, and this procedure has been used at the Athens State General Hospital not only in cases of ruptured ectopic gestation but in every case of intraperitoneal hæmorrhage

I remember a patient with a stab wound who immediately after the opening of his abdomen under local anæsthesia received more than 200 ml. of his own blood before it became evident that his stomach had a perforating wound from which gastric juice was leaking out. The patient developed no reaction whatsoever after this erroneous autotransfusion, and under penicillin cover only he made the smoothest post-operative recovery

During the same period we also used autotransfusion successfully during aseptic major operations involving accidental or inevitable profuse intraperitoneal bleeding

As Mr Azie states, "this simple method could be applied by any doctor with little or no assistance in a remote hospital" I would add that although this method should be in the mind of every surgeon it should not be used when blood-transfusion facilities are available or when the aseptic condition of the intraperitoneal blood is suspect because of an intestinal injury or otherwise

Laikon Hospital,
Athens N J GEORGIADIS

SIR,—It was very pleasing to read the letter from Sir Claude Frankau in your last issue, for at that time I was in Bethune and was shifted as surgical specialist to the 7th Div clearing station at Aire close by

At the battle of Neuve Chapelle in March, 1915, and later in that of September 25, we who drained the front line opposite us, regularly used peritoneal blood for resuscitation and thought little of it, for the simple reason that for long prior to the war in my own hospital, the Eden, Calcutta, it was a hospital standing order that in every case where blood from whatever cause was extravastated into the abdomen, it should, after filtering, be reintroduced into the blood-stream The only obligation being in those days that the vessel to contain the blood should contain not less than 1 oz of 1% sodium citrate solution, and that the actual blood that was "cupped" from the belly should be filtered through not less than 12 layers of plain white gauze

I can recall hearing of Captain Fraser's success at Bethune but in the flurry of war it raised no eyebrows in the Meerut C.C S of Major Goodwin, for very shortly after, we were all waiting on the very original work of Kenneth Walker who had initiated direct blood-transfusion

Looking back over the years and recalling the tragedy of the Battle of Loos, I have no doubt whatever that we saved many lives by what in those days were dubbed by Lilliputians, "Oriental ways"

London, W 1 V B GREEN-ARMYTAGE

EVENING COLIC IN INFANTS

SIR,—Dr Tuckman's criticism (Jan 2) of the figures for the dicyclomine study are legitimate, but they omit certain other relevant data

To reiterate, of 16 babies receiving the inert substance, 8 were unaffected, and the remaining 8 were given a total score of 19, the mean score being +1 18 Of 20 receiving the active drug, only 1 was unaffected, the remaining 19 being given a total of +47, the mean score being +2 35

Three mothers found the inert substance more effective than the active drug, the total difference being +5 Nine mothers found the active substance better than the inert one, the total difference being +20

Five mothers stated that one bottle was useless, and the other very effective, and in each case the one considered useless contained the inert substance

I think that my conclusion that the drug is of value is justified

The University of Sheffield
Department of Child Health,
The Children's Hospital,
Sheffield R S ILLINGWORTH

INTESTINAL ABSORPTION OF VITAMIN B_{12}

SIR,—The paper [1] by Reizenstein and Nyberg on the intestinal absorption of liver-bound radiovitamin B_{12} was of especial interest to us in relation to current studies in our laboratory with 5, 6-dimethylbenzimidazolyl cobamide coenzyme ("coenzyme B_{12}") *

Barker's group, which isolated this material from liver, presented evidence suggesting that this coenzyme B_{12} may be the metabolically active form of vitamin B_{12} as well as the main storage form in the liver [2] The possibility was raised that this material might be absorbed from the intestine more readily than vitamin B_{12} in the absence of intrinsic factor

Our preliminary studies with "coenzyme B_{12}" suggest that

(1) In vitro, coenzyme B_{12} appears to compete with vitamin B_{12} in a 1 1 ratio for attachment to intrinsic factor on liver homogenate receptors

(2) Patients with pernicious anæmia in relapse show optimum hæmatological and clinical responses to the daily intramuscular injection of 1 μg of either coenzyme B_{12} or vitamin B_{12} At this intramuscular dosage level, coenzyme B_{12} and vitamin B_{12} appear equal in their effects

(3) The absorption of small (2 μg) oral doses of radioactive coenzyme B_{12}† appears to be less dependent on intrinsic factor than the absorption of similar doses of vitamin B_{12} itself as suggested by our preliminary studies with Schilling-type testing [3] using ^{57}Co coenzyme B_{12}

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* Supplied to us by Dr H A Barker, Department of Biochemistry, University of California Berkeley 4, California and Dr David Perlman, Squibb Institute for Medical Research New Brunswick, N J

† The radioactive ^{57}Co coenzyme B_{12} was obtained through the courtesy of Dr David Perlman, Squibb Institute for Medical Research, New Brunswick, N J

1 Reizenstein P G Nyberg W *Lancet* 1959, ii, 248
2 Weissbach, H , Toohey, L , Barker, H A *Proc Nat Acad Sci* 1959, 45 521
3 Ellenbogen, L , Williams, W L. *Blood*, 1958, 13, 582

We would speculate that the liver-bound B_{12} of Reizenstein and Nyberg and coenzyme B_{12} of Barker may be the same substance Further studies are indicated to test both this possibility and the possibility that coenzyme B_{12} may be less *intrinsic-factor*-dependent for intestinal absorption than vitamin B_{12} itself

New York City

Louis R Wasserman
Solomon Estren
Eugene Brody
Victor Herbert

RADIOLOGY IN PERNICIOUS ANÆMIA

Sir,—We should like to correct two points in your annotation "Gastric Outline and Motility" (Jan 2) concerning our radiological findings in the stomach in pernicious anæmia On examining 69 patients with pernicious anæmia in remission we found, in 53, a combination of features which we believed indicated gastric atrophy (not gastritis) These were, as stated, a smooth tubular longitudinal gastric segment, a smooth fundus devoid of normal folding, fine "crushed tissue-paper" rugæ in the empty longitudinal part of the stomach with normal rugal pattern in the transverse part The stomachs were of small volume and emptied rapidly so that they could not be distended This was partly due to the peristalsis which was quite active and not poor, as stated in your annotation We think this point is important because in the only case in the series where peristalsis was absent in the body of the stomach a "leather bottle" type of carcinoma of the stomach was present Details of the findings in these patients with pernicious anæmia and in the control group are awaiting publication [1]

Radiodiagnostic Department,
Hammersmith Hospital,
London, W 12

J W Laws
R G Pitman

OBESITY

Sir,—Dr McMullan in his letter of Jan 2 writes "There is nothing inherently improbable in the idea that certain people—even most people—are able to respond to excessive food intake by increased metabolism" This thesis was set out nearly 50 years ago by Grafe,[2] who postulated such a *luxus Konsumption* mechanism since then, it has been widely discussed but has received no satisfactory experimental support I used to think that it was probably correct and five years ago with some colleagues tried to get good evidence to confirm the thesis

We [3] gave three constitutionally thin young men diets containing 1300-1600 calories in excess of their requirements for periods of 10-14 days During this time they followed a standard regime in a metabolic ward Metabolic-rates were determined by indirect calorimetry at 4-hourly intervals throughout 24-hour periods There was no evidence that any of the excess food was oxidised, apart from a small amount due to the rise in metabolism attributable to the specific dynamic action of the extra protein eaten There can be no doubt that these three young men possessed no *luxus Konsumption* mechanism

In the continued absence of any positive experimental support for this thesis, it seems unlikely that normal people possess an ability to metabolise directly any dietary excess

Department of Physiology,
University of Edinburgh

R Passmore

POSTOPERATIVE DIARRHŒA

Sir,—Mr Shipman (Dec 12) points out that, once diarrhœa has commenced, the transit time of methylene-blue through the bowel is shortened

The transit time should be accepted with caution, owing to the rapidity with which methylene-blue diffuses through a liquid medium The only explanation of the continuing dilatation of the bowel in these patients is the presence of some degree of "hold-up" or stasis of the intestinal contents

But it is the state of the bowel before the onset of the diarrhœa which is important from the ætiological point of view In my cases, there was a highly significant association between intestinal stasis and the subsequent development of diarrhœa. During the period of stasis, constipation was almost invariable, so it was not possible to estimate the transit time through the bowel

Victoria Infirmary,
Glasgow

Graham Schofield

FLOW-METER FOR EXTRACORPOREAL CIRCULATION

Sir,—We were interested to read of the extracorporeal-circulation blood flow-meter described by Dr Nixon (Nov 14) Several of our associates have made similar suggestions, but we do not agree that such a device gives a reliable guide to the blood flow-rate under clinical conditions, although it makes a useful alarm for high line pressures

During 65 experimental and clinical cardiopulmonary bypass procedures, we have noticed fluctuations of up to 100 mm Hg in the line pressures while the flow-rate remained constant An occlusive setting has been used on a De Bakey pump on $^{3}/_{8}$ in or $^{1}/_{2}$ in internal-diameter 'Tygon' tubing to pump flows of 80–120 ml per kg per min through cannulæ 3–5 8 mm × 4 cm for procedures lasting up to two hours Mean arterial blood-pressure was monitored in an internal mammary or branchial artery by a pressure transducer and ranged from 85 to 100 mm Hg, while line pressures ranged from 180 to 380 mm Hg

In the laboratory the pressure drop is indeed due to the constriction of the cannula, but in the body an important factor is vascular tone, especially as it affects the artery directly adjacent to the cannula Should the flow rise over approximately 3 litres per min in $^{3}/_{8}$ in internal-diameter tubing, the change to turbulent flow will cause a disproportionately large increase in the pressure measured at the filter-chamber

Department of Anesthesiology,
Hartford Hospital,
Hartford, Connecticut

I A Sloan

INFLUENZA AND HEART-DISEASE

Sir,—I should like to refer to Dr Bourne and Dr Wedgwood's paper [1] on heart-diseases associated with influenza, and to Dr Apley's letter [2]

We have observed a respiratory infection in a native male child of $2^{1}/_{2}$ years which we considered as influenza because it occurred at the tail-end of an epidemic, and also because the histopathological findings in the lungs and heart suggested a viral infection The child developed congestive heart-failure in the second week of his illness and died from it

This might be of interest to people who have investigated the association of heart-disease with influenza, so we submit briefly the pathological report by Dr T H Vickers, of the University of Queensland

Lung —There is slight hæmorrhagic consolidation of lung parenchyma with probable œdema and a peribronchial mononuclear-cell infiltration Patchy intra-alveolar phagocytes are seen in some fields and the alveolar walls are rather thicker than normal suggesting the existence of mild passive congestion As well there is evidence of a lobular pneumonia of indeterminate type

Heart —There is probable hypertrophy of most muscle fibres in

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[1] Laws J W Pitman R G *Brit J Radiol* 1960 (in the press)
[2] Grafe, E Graham, D *Hoppe Seyl Z* 1911, 73 1
[3] Passmore R Meiklejohn, A P, Dewar, A D, Thow, R K *Brit J Nutr* 1955 9 20

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[1] Bourne, G Wedgwood, J *Lancet*, 1959, i, 1226
[2] Apley, J *ibid* p 1282

the heart and undoubted hypertrophy of some, so that the cardiac enlargement can be regarded as due to an increase in the bulk of the myocardial fibres and probably not due to œdema This hypertrophy is accompanied by a slight but patchy mononuclear-cell infiltration most marked in the connective tissue around some of the blood-vessels and in the subserosa The cellular infiltration is much more suggestive of a very mild myocarditis than an ischæmic lesion

Department of Public Health,
Mount Hagen,
Western Highlands District,
Territory of Papua and New Guinea
L E PETRAUSKAS

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—It was sad to see Dr Simpson's valuable and careful analysis of hæmangiomata (Dec 12) receive such hostile criticism in recent letters Dr Colin-Jones (Jan 2) writes airily of "misleading statistics", but cannot show that Dr Simpson's observations (or deductions) were in error He says "large numbers must be studied", but quotes with approval a series of 135 untreated cavernous lesions, while the paper he criticises deals with a slightly larger number He himself reports 814 cases which received X-ray therapy, he mentions that 200 required treatment "after the 5-year period" but he is curiously vague about the precise results He further confuses his own position by saying in one place "all are agreed that cavernous angiomas disappear in the course of time", but a little later he thinks "there is a great tendency to exaggerate the frequency"

Dr Simpson has in fact much well-informed dermatological opinion on his side, he also has the support of most plastic surgeons who, reluctant to carry out operative treatment which may give inferior results to those achieved by natural regression, still insist that the child is kept under close observation, they are thus in a position to intervene on rare specific indications What plastic surgeons dread most in this context are the horrifying results which can follow the improper use of radiotherapy to "cure" non-malignant lesions in the young

The Queen Victoria Hospital,
East Grinstead
C R MCLAUGHLIN

SIR,—It is apparent from the letters of Dr Colin-Jones and Mr Denis Browne (Jan 2) that Dr Simpson has a hard task ahead if he wishes to convert all the treaters of cavernous hæmangiomata into non-treaters

I am sure that his policy of no-treatment is a wise one although it requires far more courage and persuasion on the part of the clinician to convince anxious parents that nothing should be done

In Sheffield, for the past ten years, all the dermatologists have adopted a no-treatment policy for cavernous hæmangiomata. It has, therefore, been impossible for patients to leave one clinic and go to another where they would be treated The radiotherapists, who include Dr Walter, the author of a controlled trial [1] of radiation and no-treatment in 1953, have carried out the same policy The only escape route for dissatisfied patients has been to the department of plastic surgery, and I understand that there has been no rise in the number of cases referred for operation during the ten years

The dermatologists and radiotherapists have watched spontaneous clearing occur in the great majority of the cases and they amount to some 200 hæmangiomata per year Resolution has been particularly striking in those cases which, by their size or site, give rise to the biggest problem and which present a formidable task for surgeon or radiotherapist. There are no extra hazards from awaiting spontaneous resolution and the cosmetic results are as good, if not better, than any form of treatment There are dangers from radiation, for in the series of carcinomas of the thyroid reported by Wilson et al [2], 4 had received radiation for nævi around the neck. There is also no evidence that radiation does more than slightly speed up natural resolution

Dr Colin-Jones' remark that hæmangiomata are common in adults is difficult to understand since that is certainly not the experience in this area I believe that, as yet, no form of treatment is superior to spontaneous regression though it would be interesting to hear more of the results of Mr Denis Browne's early surgery

The Rupert Hallam Department
of Dermatology, Royal Infirmary,
Sheffield
I B SNEDDON

SIR,—It would be helpful if Mr Denis Browne would kindly clarify one or two points he has raised in his comments on the views of Dr Simpson and others who have worked along the same lines before him

With regard to the first statement that many dreadful disfigurements begin as tiny red spots either present at birth or appearing in the first month, could he produce evidence that the large disfiguring hæmangiomata do often grow from tiny strawberry marks? I have watched for the development for years and have never seen it happen, assuming therefore that the deeply situated hæmangiomata must arise subcutaneously Be it noted that only one type of hæmangioma is discussed in Dr Simpson's paper, "port wine" and systematised nævi being rigidly excluded

Next he states categorically that in their earliest stages hæmangiomatous nævi are quite invariably dismissed as trivialities, but he does not say by whom Does he mean parents, general practitioners, or dermatologists, or all three? The long and meticulous follow-up studies by dermatologists to which he refers in his opening remarks indicate at least that some dermatologists have accepted these nævi as a very serious responsibility

Finally he says that while no early case has ever been referred to him by a general practitioner, "in spite of his preaching that a growing red spot on a baby's face is a surgical emergency", he has picked up a few and treated them The results, he says, suggest that the process of regression can be started very early in the growing stage by producing inflammation in the abnormal tissues Could he possibly enlarge on this experience and tell us what he does? Most of the dermatologists have discarded diathermy, cauterising, and the injection of chemical substances because they, to whom these cases are referred in numbers by practitioners, have found such methods unsatisfactory It is precisely this fact that has prompted the natural-history studies during the past twenty years Freezing for small strawberry nævi is evidently acceptable to some, but the outlook in these nævi when not treated has long been known to be so good that many think it wiser to let well alone Few will use any kind of radiotherapy in infants except when it can hardly be avoided Is there something else about which we have not heard?

London, W 1
G B DOWLING

SIR,—The essential point at issue in this discussion is surely a simple one—is there any real risk involved in treating all cavernous nævi with X-rays or thorium X, because if there is no risk, it is surely the best policy to give all affected children the benefit of treatment until the day when it is possible to distinguish at an early stage between those lesions which are likely to resolve spontaneously and those which will persist

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[1] Walter, J *J Fac Radiol* 1953, 5, 134

[2] Wilson, G M, Kilpatrick, R, Eckert, H, Curran, R C, Jepson, R P, Blomfield, G W *Brit med J* 1958, ii 929

I have been irradiating nævi for nearly twenty years, having initially used what would now be regarded as a rather high dose of 600–800r at 100 kV, repeated after three months, but I have yet to see or hear of any permanent ill effect among my treated cases, numbering over 1000, including those treated in association with Dr Colin-Jones In a confined community such as this, one would expect to be made aware of any untoward sequelæ of treatment, and colleagues would not continue to refer cases were they not completely satisfied

There is at present a swing away from the use of radiotherapy in non-malignant conditions, particularly in children, and while it is wise to keep in mind the hazards attending the irradiation of living tissues, few methods of treatment contain no possibilities of causing damage if improperly used, and it would be a great pity if patients of any age were to be deprived of beneficial treatment because of unjustified fears engendered by propaganda The dosage given to a child with a nævus is less than would result from many X-ray examinations, measured as total-body dosage, and the local dose used now, of the order of 400r at 60–100 kV on small fields, has not shown any late changes in the skin, hair, or bone

May I conclude that we should continue to use our clinical judgment in dealing with nævi and that we should not be swayed against active treatment by doubtful hopes of natural resolution

Hove E Millington

Sir,—The article by Dr Simpson and the subsequent correspondence indicate the confusion which is caused by the terminology of hæmangiomata

When Dr Simpson talks about " cavernous hæmangioma " he is presumably referring only to the common " strawberry nævus ", a lesion which is typically confined to the skin, and we are in entire agreement with him that these lesions will always regress spontaneously and that no treatment is necessary Since they always disappear spontaneously, it follows that any form of treatment will be credited with good results It seems unlikely that injection of sclerosing substances, treatment by carbon-dioxide snow, and similar methods will result in harmful sequelæ, but in view of the late, serious, and quite unpredictable consequences of treatment by radiotherapy, it seems to us that the use of such a powerful agent is highly undesirable and can be justified only in the most exceptional circumstances

We cannot agree with Dr Colin-Jones that " strawberry nævus " is commonly seen in adults None of the surgeons in this centre has ever seen such a lesion, although we have seen many other types of angiomata in adults If Dr Colin-Jones has failed to distinguish the different types of hæmangioma, the results of his treatment are impossible to evaluate

We strongly advocate that the term " cavernous hæmangioma " should not be used for these common skin lesions, but that they be described by the homely but unmistakable term " strawberry nævus"

I F K Muir
T L Barclay

Mount Vernon Centre for Plastic Surgery,
Northwood, Middlesex

ATRIAL FIBRILLATION IN CARCINOMA OF THE LUNG

Sir,—The association of arrythmia with carcinoma of the lung has prevously been noted, but the following case seems worth recording to stress the importance of what appears to be a little-known manifestation of the commonest form of cancer [1 2]

A man of 55 complained for one year of dizziness on exertion, associated more recently with attacks of regular palpitations, beginning and ending suddenly He admitted to cough and pain in the shoulder for the previous fortnight but had no other significant symptoms He had atrial fibrillation, with an apex rate of 120 and a pulse deficit of 16

The chest showed flattening and diminished movement in the left upper zone, with an impaired percussion note, diminished breath sounds, and a persistent localised rhonchus There were no other significant physical findings

A clinical diagnosis of bronchial carcinoma was made on the basis of the association of signs of left upper-lobe collapse with atrial fibrillation

Radiography showed a large left hilar mass with upper lobe collapse and a trace of fluid at the left base Tomograms demonstrated almost complete occlusion of the left upper-lobe bronchus Electrocardiography showed uncontrolled atrial fibrillation Repeated sputum examination for malignant cells was negative

An attempt to restore sinus rhythm with quinidine succeeded only for a few hours, after which ventricular tachycardia supervened It was therefore decided to slow the ventricular rate with digoxin.

His general condition deteriorated rapidly and he developed massive hepatomegaly and bloodstained ascites A further E C G before death showed that runs of atrial extrasystoles had developed, with varying PR interval

He died seven weeks after first being seen Necropsy confirmed the diagnosis The growth arose in the left main bronchus and invaded the left atrium and compressed the left pulmonary vessels The heart was otherwise normal There were massive deposits in the liver

There are two especially interesting features of this case

(1) The fact that atrial fibrillation was the presenting feature

(2) The fact that apart from the fortnight of cough and shoulder pain before attending outpatients, there were no respiratory symptoms throughout the course of the illness

Since this patient was seen, I have seen a further case in which atrial fibrillation arose in a 75-year-old man with signs of left lower-lobe collapse He deteriorated rapidly, and necropsy revealed a carcinoma of the lung which had invaded the pericardium and myocardium There was no coronary atheroma

My thanks are due to Dr R A Hickling for his encouragement and for his permission to publish this account of his patient I should also like to thank Dr H P Clarke for making it possible for me to visit the patient at home

London, N 10 W L Ashton

DIURNAL FLUCTUATIONS OF PLASMA FIBRINOLYTIC ACTIVITY

Sir,—Readers of the articles by Buckell and Elliot [1 2] may be interested in the following observations

The diurnal fluctuations of fibrinolytic plasma activity were observed independently in our laboratories, and first described two years ago [3–6] The fluctuations of fibrinolytic activity were tested on diluted oxalate plasma and euglobulins clotting with Ca++ addition and, furthermore, on thrombin clots of oxalate euglobulins, which do not form intrinsic thrombin Samples of citrate-thrombin, free of plasma, were used The daily fluctuations of fibrinolysis were most pronounced in the thrombin clots of oxalate euglobulins The titre of antifibrinolysin did not fluctuate adequately in samples of plasma and sera taken during the day The antifibrinolysin was tested on a system consisting of bovine plasma, fibrinogen, and citrate-thrombin. The titre was found to vary from 50 to 87 arbitrary units in samples of plasma taken in the morning and from 46 to 88 in samples taken at the height of the fibrinolytic

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[1] Fishberg, A M *Amer J med Sci* 1930, 180, 629

[2] Levy, T M *ibid* 1948 36, 312

[1] Buckell, M , Elliot, F A *Lancet*, 1959, i, 660

[2] Buckell, M , Elliot, F A *ibid* p 662

[3] Kaniak, J , Siwińska, M , Krakowska-Rechnicowa J , Iwankiewicz S., Kornaszewski, W *Postępy Higieny i Medycyny Doświad zalnej*, 1957, 11, 355

[4] Kaniak, J , Siwińska-Kotschy, M , Głogowska, I *ibid* 1958, 12, 299

[5] Siwińska-Kotschy, M , Głogowska, I *ibid* p 533

[6] Kowarzyk, H., Kotschy, M , Głogowska, I *ibid* 1959, 13, 315

activity The respective figures in serum were 51 to 76 and 43 to 70 units Thus, changes of the antifibrinolytic titre do not seem to be the cause of the diurnal fluctuations of fibrinolysis

The highest activity of fibrinolysis was comparable to that observed in an emergency reaction after adrenaline and in a hypoxæmic state at low air pressure The diurnal fluctuations are a stress reaction and they vary from person to person and in the same individual from day to day The diurnal fluctuations do not appear in young males confined to bed—e g , with fractures

T.A.M. (tosyl-L-arginine methyl ester HCl) esterase activity of plasma and serum does not fluctuate correspondingly

Diurnal fluctuations may mask the effect of alimentary lipæmia on fibrinolysis[7] When comparing small groups of persons examined with the euglobulin and diluted plasma-technique at fixed hours of the day, one fasting, the other one after a fat meal, no significant differences of fibrinolytic activity were found between the lipæmic and control groups, the diurnal fluctuations of lysis time being invariably superimposed on the presumed lipæmic effect. Our main interest was in the activating mechanism of fibrinolysis, and no further attempt was made to verify the effect of lipæmia on fibrinolysis

The fibrinolytic activity of globulins from diluted and acidified human plasma is potentiated by the process of thrombin formation[8,9] The time of fibrinolysis is shorter in spontaneously clotting euglobulins than in the thrombin clot of the euglobulins not forming intrinsic thrombin The time of lysis, in our operative conditions, averaged 210 and 450 minutes respectively In stress, the time of lysis of thrombin clots is decreased to about 160 minutes In the state of increased fibrinolysis, however, the generation of thrombin does not induce a further rise of fibrinolytic activity Thus, the fibrinolytic activity developed in stress obscures the fibrinolytic activity related to thrombin formation

The data so far available support the view that a uniform activating mechanism acts in vivo in the fibrinolytic stress reaction and in vitro in thrombin-forming fibrinolytic systems

Ludwik Hirszfeld's Institute of Immunology and Experimental Therapy, Wroclaw, Poland

HUGON KOWARZYK
JÓZEF KANIAK
MARIA KOTSCHY

HOTELS OR HOSPITALS?

SIR,—I read with interest the article by Mr Stallworthy (Jan 9) on the subject of "hotel" accommodation following operation Thanks to a generous benefactor, it was possible in June of last year to open a "continuation" unit attached to Kilmarnock Infirmary It is hoped to publish at the end of a year's work of this annexe a full report of the economic and clinical advantages

The building, now called Torrance House, is a former sanatorium, and has been converted into very comfortable "hotel" accommodation with adequate rest and recreation rooms and dining-rooms Beds are available for 44 patients, at present allocated between general surgery (28) and general medicine (16) The 28 surgical beds are filled from 60 surgical beds in the parent hospital, which is within ten minutes' distance by ambulance Patients are transferred to Torrance House as soon after operation as it is thought that they are fit to walk from the sitting-rooms to the dining-rooms Thus hernia repairs, appendicectomies, and hæmorrhoidectomies are normally transferred on the second or third postoperative day, and gastrectomies, vagotomies, and cholecystectomies on the fifth day There is no routine transfer, the fitness of the patient for the annexe is assessed on the day before the transfer The patients are transported by ambulance from the parent hospital, and throughout their stay in the annexe they wear their own clothes

No medical staff is resident in the annexe, but a direct telephone line to this parent hospital means that a house-surgeon is on immediate call. Nursing staff consists of one matron, two sisters, two full-time and two part-time staff nurses, two full-time auxiliary nurses, and four part-time assistant nurses

During the short time that Torrance House has been in action the advantages set out by Mr Stallworthy have become apparent In the first six months 620 patients were transferred to the surgical beds from Kilmarnock Infirmary with the result that the general surgical waiting-list has come down in that time from 460 to 310 after years of being static or rising The comfort, quietness, and access to gardens is appreciated by the patients, and early return to complete activity is hastened. It is surprising how well a fifth-day gastrectomy can play billiards!

No serious disadvantages have been encountered, but a certain self-discipline is required by those in charge of beds in the "hotel" As far as Torrance House is concerned, it has been written into the constitution that the maximum stay for patients is three weeks—this to prevent any temptation to use beds for chronic sick. We have made it a routine here for all surgical patients in the annexe to be seen daily by a consultant together with the registrar or a house-surgeon. This is necessary, not only for the purpose of clinical supervision, but in order to avoid giving the patients the impression that they are being "dumped" out of the main hospital

The Infirmary,
Kilmarnock

GAVIN J RALSTON

SIR,—How heartening to see in last week's *Lancet* a really imaginative article on the future planning of a hospital and home-care service There are a good many nurses who also believe that the future of our health service will lie in acute central hospitals for the individual who needs and must have hospital care, plus convalescent aftercare units run on hotel lines, and a really well-organised, well-staffed domiciliary medical and nursing service

One visualises "flying-squads" of nurses and doctors visiting people in their own homes, doing dressings, treatment, and so on. The "squads" would be based on the local authority What a wonderful opportunity to train nurses and doctors! At present one of the most common criticisms levelled at our nurse-training by other countries is that British nurses "only nurse in hospital", a criticism that cannot be denied but with the kind of service envisaged, trainee nurses and medical students alike would get immensely valuable training in caring for people in the ordinary social setting of their homes a broadening and educational experience we could all do with early in our career The acute centres would, of course, deal with all conditions requiring hospital care, for whatever cause. Again, the ideal training situation, where the student can have experience of all human ills under one roof—a really comprehensive training, with plenty of chance to specialise later

For so long now I have thought about this idea as a sort of unattainable pipe-dream, regarded as fantastic if expressed, that it is really exciting to see it has already taken shape in other minds, though perhaps it is a little ironical that it has taken us about two hundred years to persuade people that hospital is the best place to be ill in, and now that this idea seems to have been well and truly sold to the suffering public there are signs of a move to re-educate them to prefer to be ill at home. Somehow I think the process is likely to take less time

Tooting Bec Hospital,
London, S W 17

UNA V BUDGE

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[7] Greig H B W *Lancet*, 1956, ii, 16

[8] Kowarzyk, H 6th Congress of the European Society of Hæmatology, Copenhagen, 1957, ii, 452

[9] Kowarzyk, H., Buluk, K *Postępy Higieny i Medycyny Doświadczalnej*, 1959, 2, 1

Obituary

WILLIAM ROBERT FEARON

M.A., M B, Sc.D Dubl, F R I C

Professor Fearon, who held the chair of biochemistry in the University of Dublin and was a member of the Irish Senate, died on Dec 27 at the age of 67

His father, the Rev William Fearon, of Kells, died when he was a child and he was brought up by his mother From St Andrew's College, Dublin, he entered Trinity College in 1911 and started his medical studies soon afterwards But he was such a versatile student (winning with equal ease medical scholarships, the Purser medal in physiology, and the vice-chancellor's prize in English verse, and taking an honours degree in the natural sciences) that he did not finally qualify till 1929 Meanwhile he had spent two years with an exhibition at Emmanuel College, Cambridge In 1921 he was appointed to a fellowship at Trinity College, Dublin There, though his chief duty was teaching physical chemistry, physiology, and biochemistry, he also gladly gave lectures in logic and examined in that subject But the influence of Werner in Dublin and Gowland Hopkins in Cambridge had already determined him to make biochemistry his chief interest He was appointed lecturer in 1921, and in 1934 a chair was created for him In the same year the first edition of his well-known *Introduction to Biochemistry* appeared. Even with growing academic responsibilities his interests in the arts did not slacken, and his play *Parnell of Avondale* was successfully produced at the Abbey Theatre in 1937

Some of Fearon's earliest biochemical work was related to urea, which was Werner's special interest, and to vitamins But it was not long before another side of his nature began to express itself in his work He was early elected honorary professor of chemistry to the Royal Hibernian Academy, and his love of colour, as of the artistic, combined to make him an ideal choice In his scientific work the charm which colour held for him began to express itself in the development of a series of colour reactions for the identification of a wide range of compounds of biological interest

In 1943 he was first chosen by the university electorate as their representative in the Irish Senate

R A Q O'M writes

"Of his election to the Senate, Fearon was very proud and, curiously, this honour provided him with more pleasure and satisfaction than many others which he had won during his distinguished career The university electorate continued to the end to return him and, in the special circumstances which govern this election, his repeated return signified that his former students supported him with their first preference votes almost to a man Of course, he drew support from other sources as well, but no doubt the memory of his inspired teaching must have remained to prompt them as they marked their voting-papers His lectures were memorable not alone for their scientific content but for the beauty of the language and the clarity of expression, enlivened by artistic, musical, theatrical, and poetic reference, with which they were delivered, and when he spoke in the Senate his audience was likewise held. Standing at Fearon's graveside an elder of the House, well tried in politics, said, 'He could make a speech He had a nice wit and a sense of irony, too'

"His wit and irony, never malicious though often happily pointed, were a charming asset to Fearon at the table or on the platform He was much sought after on such occasions as opening meetings of societies or when the time had come to lionise the distinguished visitor He appreciated good food and wine, but as time went by he became more difficult to entice to the festive occasion. Great was the reward of success in such enticement, however, for an evening in his company never flagged Even the chance and seemingly aimless remark of the least important of the guests was likely to be taken at more than its value and built by him into a subject for serious consideration in a happily light vein For it was one of his characteristics that he was always ready to listen to others, to see good in their often faltering thoughts and gently to amplify them so that they rapidly grew, like a tree, to have many branches

"Fearon remained a bachelor He lived with his mother, to whom he was greatly attached, and who died only a few years ago His home life was simple, though he had one inclination to extravagance—in his cars In the 'twenties he could be seen as the sole occupant of a long Lancia, later of a Bentley, and in the final years, as befitted his Senatorial rank, of a Rolls Towards the end it was apparent that he was becoming dissatisfied with the crudities of modern life and in particular felt unhappy about the decline in manners in our times His was a generous, courteous, and upright nature, and he was incapable of the rudely aggressive or of the plausibly dishonest For him 'the larger heart, the kindlier hand'"

Dr J E A UNDERWOOD

R E S writes

"The Medical Officers of Schools Association owes Dr Underwood a particular debt. He realised that, though doctors at public schools had for a long time usually occupied the important offices, the association had the welfare of all types of boys and girls at heart. He was the first senior official of the Ministry of Education to take an active part in our discussions and the first to become president (in the 68th year of our foundation) From 1952 to 1953 he presided with great dignity and we came to know that behind his humility lay great knowledge especially of the handicapped child His name will be remembered in many ways but it will live chiefly for the Underwood report on the maladjusted child"

Public Health

Safety Code for Use of Ionising Radiations

REVISIONS to the draft code, issued in July, 1957, for the protection of workers engaged in operations involving the production, emission, or use of sealed sources of ionising radiations are contained in the second preliminary draft of special regulations [1] published this week.

The original draft included a general invitation to industry, associations, and others concerned to make comments on the proposed regulations, and many suggestions were received and amendments arising from the observations have been included in the new draft

The schedule specifying the maximum permissible radiation doses has been remodelled taking account of the views of the Medical Research Council and the revised recommendations of the International Commission on Radiological Protection It has been simplified by restricting it to certain ionising radiations which are ordinarily met with in industrial work with sealed sources There are new provisions dealing with tests for personal exposure and medical supervision, with the examination of persons employed in the processes, and the procedure to be adopted where workers employed in the processes move from one factory to another Fuel elements used or intended to be used in a nuclear reactor will not be covered by these regulations, which also exclude from their application ionising radiations used for medical purposes in factories or rooms specially set apart Comments on the new draft are requested by April 15

Arsenites in Agriculture

Mr John Hare, Minister of Agriculture, Fisheries, and Food, has announced that the use of alkali arsenites in agriculture is to be restricted Speaking at Wells on Jan. 6, he said

"The potential risks here are particularly wide because of the large number of people involved and the danger to cattle The Advisory Committee on Poisonous Substances, which deals with agriculture and food storage, recommended that their use should be voluntarily banned agreement has now been reached that the manufacture of alkali arsenites for use in this country as haulm destroyers and weed killers shall now stop, and that after this year's potato harvest the agricultural and ancillary industries will withdraw these arsenites from agricultural use This voluntary ban will not apply to sheep or cattle dips, or to the use of lead arsenate on fruit trees'

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[1] Factories (Ionising Radiations) Special Regulations Second Preliminary Draft H M Stationery Office Pp 20 1s 3d

Notes and News

RESEARCH ON INTERFERON

A SUBSTANCE "with many of the properties of a wide-spectrum viral antibiotic", interferon was discovered at the National Institute for Medical Research during study of the virus interference phenomenon.[1] In his investigations with colleagues, Dr Alick Isaacs has shown that it is a protein, of low toxicity to tissues, which is apparently non-antigenic and able to inhibit the growth of a large variety of viruses. Two papers on its action appeared in our columns last September.[2]

Before the possible therapeutic use of interferon could be studied, much basic research on its properties had to be done, but a stage has now been reached when the development work that must precede therapeutic trial can be undertaken. So as to get an answer quickly, the Medical Research Council have entered into an arrangement for collaborative research with three firms in the pharmaceutical industry—namely, Glaxo Laboratories Ltd., Imperial Chemical Industries Ltd., and the Wellcome Foundation Ltd.—the National Research Development Corporation also being a party to the agreement. The work covered by the agreement includes research into the pilot-scale production of interferon required for research purposes and studies of its effect in experimental virus infections of animals. Whether it is used in therapeutic trials in human beings will depend on the results of these experiments.

A NEW INSTRUMENT

THE official existence of the new organisation and methods unit of the Ministry of Health is a sign that work study has been accepted as an effective aid to the administration of the National Health Service. Skill in using new tools usually increases with practice, and in work study the relatively close-knit hospital services will probably be easier terrain than, say, the diffuse and often highly individual arrangements hopefully covered by the orderly title of "general medical services". The National Association of Hospital Management Committee Group Secretaries have, therefore, been considering work study in the hospital service.[3] They are firmly in favour of its adoption because they believe that properly applied it may save some money (though not perhaps so much as expected, for it will sometimes lead to redeployment rather than reduction of resources) and that it will also encourage the staff to take a more informed interest in their work and often improve their working conditions. It will provide badly needed facts on priorities and needs for capital development.

The report suggests that one of the common objections to work study—that it impairs staff morale—is caused by faulty application. With tact and the right approach this difficulty should usually be avoided. Nor should work study properly conducted bring a risk of reducing services to patients, for a rational assessment of the activities of a hospital should recognise such small acts as cups of tea and reassuring talks with patients and relatives as part of a good nurse's true duties. On their frank appraisal of these difficulties is based the Association's recommendation that the most suitable subjects for work studies, at least at first, are the indirect services to the patients, such as laundry and catering, and the nonclinical organisation of other parts of the hospital such as appointment systems or records. Judging by the reports already issued this policy has been accepted by the Ministry's unit.

Difficulties would also be avoided, the Association suggest, if the study was conducted from within the hospital rather than from without, by someone who understands the background and is familiar with medical and nursing problems. In their view it should be done at H.M.C. level, and all senior hospital staff members should attend short courses on work study, and selected officers, of at least senior administrative grade, who would actually conduct the studies should attend a three-month course. It will be interesting to see how other hospital authorities, such as regional hospital boards and the Ministry, react to this last suggestion. Certainly much of the rest of this thoughtful report will win their approbation.

AMATEUR BOXING

A HANDBOOK lately issued by the London Amateur Boxing Association[1] is short but not everywhere clear or to the point. What is clear, however, is that the Association considers that the risks of boxing are not serious. The statement that "boxing represents the only opportunity in man of observing repeated head injuries in an almost experimental setting" presumably implies that the "experiment" should continue until the effect of these injuries on the brain can be fully and accurately assessed. But is this "experiment" either justifiable or necessary? Is there not overwhelming evidence that even trivial head injuries can cause serious brain damage? The boxer is exposed to injuries which are deliberate, repeated, and often severe enough to cause loss of consciousness. If the nature and extent of the damage they cause has not yet been accurately assessed, should we not, nevertheless, give the brain the benefit of any doubt? Enlightenment of the public on the dangers of boxing can come only from the medical profession, and an authoritative statement by a detached body of medical experts would do much good.

NUTRITION IN AFRICA

IN Angola in 1956, the Commission for Technical Cooperation in Africa South of the Sahara held a conference on nutrition. The second volume of the report of this conference,[2] written in French, English, and Portuguese, deals with improvements of national diets with protein-rich foods, agriculture and nutrition, public-health services and education in nutrition, treatment of ariboflavinosis in schoolchildren, the digestibility of cassava, and many other subjects. Though the many authors and different styles of presentation make it difficult to read, it contains much valuable information, and a small but useful index makes it a good reference for nutritional problems in Africa.

University of London

Dr G. V. R. Born, research officer at the Nuffield Institute for Medical Research and departmental demonstrator in pharmacology in the University of Oxford, has been appointed to the Vandervell chair of pharmacology tenable at the Institute of Basic Medical Sciences.

Dr Born qualified M.B. at the University of Edinburgh in 1943. Subsequently he entered the R.A.M.C., in which he worked as a pathologist. He was demobilised in 1947, and the following year he went as a Medical Research Council student in research methods to Oxford, where he studied the bacteriolytic enzymes of *streptomyces*. From 1951 he was for two years a member of the Council's scientific staff, working in the toxicology research unit at Carshalton. He returned to Oxford in 1953. He graduated D.PHIL. at Oxford in 1951, and M.A. in 1956. Dr Born's published work includes papers on smooth muscle and on blood platelets, and a chapter on the effects of injury on metabolism in Florey's *General Pathology*.

Dr D. L. J. Bilbey, assistant professor of anatomy in the University of Toronto, has been appointed to a readership in anatomy tenable at King's College.

Dr R. M. H. McMinn, lecturer in the University of Sheffield, has been appointed to a readership in anatomy tenable at King's College.

University of Liverpool

A symposium on general practice and psychiatry will be held on Saturday, March 26, at 10 A.M., in the University New Medical School, Ashton Street, Liverpool. Tickets may be had from the director, Department of Studies in Psychological Medicine, 77, Bedford Street South, Liverpool, 7.

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[1] Isaacs, A., Lindenmann, J. *Proc. roy. Soc.* B, 1957, 147, 258.

[2] Isaacs, A., Westwood, M. A. *Lancet*, 1959, ii, 324; Porterfield, J. S. *ibid*, p. 326.

[3] Copies of the report are available from the hon. secretary, Mr S. G. Hill, LL.B., F.H.A., General Hospital, Northampton.

[1] Medical Aspects of Amateur Boxing. Issued by the London Amateur Boxing Association, 69, Victoria Street, S.W.1. 1959. Pp. 64. 2s. 6d.

[2] Vol. 2, pp. 877. Obtainable from Abbey House, 2, Victoria Street, London, S.W.1.

University of Birmingham

Dr. R F Fletcher has been appointed lecturer in medicine

University of St. Andrews

Dr John Simpson has been appointed senior lecturer in public health and social medicine in Queen's College, Dundee

Royal College of Physicians of London

On Tuesday and Thursday, Feb 2 and 4, Dr L G Norman will give the Milroy lectures He will speak on the medical aspects of the prevention of road accidents On Tuesday and Thursday, Feb 23 and 25, Prof D E Denny-Brown will give the Croonian lectures He will speak on diseases of the basal ganglia and their relation to disorders of movement All the lectures will be given at 5 P M at the college, Pall Mall East, S W 1

Royal Faculty of Physicians and Surgeons

At a meeting on Jan 4, with Mr Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship of the faculty

Majid Ali Jafri *qua physician*, Mohamed Magid Ismail Fakhr, C N Hudson, D G Jones *qua surgeon*

College of General Practitioners

Public Welfare Foundation Prize—Six prizes (£40 each) are offered to encourage senior medical students to study the diagnosis and management of patients in the setting of general practice Particulars may be had from the secretary of the college, 41, Cadogan Gardens, London, S W 3 The closing date is May 1.

International Hospital Federation

Dr J C J Burkens, medical director of the Oude en Nieuwe Gasthuis, Delft, Holland, has succeeded Captain J E Stone as hon secretary and treasurer of the Federation The secretariat remains in England at 34, King Street, London, E C 2

Medical Costs in South Africa

Dr. Albert Hertzog, the South African Minister of Health, has announced the appointment of a commission to inquire into the factors responsible for the high cost of medical services and of medicines and into ways in which these costs can be lowered The Minister said

> "Families in the middle-income group are especially hard hit On the one hand they cannot, as in the case of the less privileged, receive free medical treatment, and on the other hand they are not financially in a position to spend large sums of money on treatment It often happens that, because of the serious illness of one member, a whole family is crippled financially for years Others again neglect their health with tragic results because they cannot manage the high expenditure"

Professor J A B Gray will give his inaugural lecture on Tuesday, Feb 23, at 5 30 P M at University College Gower Street, London, W C 1 He will speak on the place of physiology in university education

The Polar Medal has been awarded to Dr R I Willing for service as medical officer to the Australian National Antarctic Research Expedition to Mawson, 1957

Dr P K Basu has been appointed the Stapells director of ophthalmic research in the University of Toronto

The Biochemical Society will hold a meeting on Saturday, Jan 23, at 10 A M at the London Hospital Medical College, Turner Street, E 1

The closing date for entries for the Jean Hunter Bequest of the Royal College of Physicians of Edinburgh (Advertisers' Announcements, Jan 9, p 37) has been advanced to June 30, 1960

The General Medical Council has published the third edition of their *List of Approved Hospitals and Institutions and Recognised House Officer Posts* Copies (7*s* 6*d*) may be had from the registrar of the Council, 44, Hallam Street, London, W 1

CORRIGENDUM *Resistance to Ketosis in Obese Subjects*—In the paper by Professor Kekwick and his colleagues (Dec 26) a sentence near the bottom of column 2 on p 1158 should read "Blood leaving the brain has a respiratory quotient of 0 97 and the rate of utilisation of glucose is about 5 5 mg per minute per 100 g brain"

Diary of the Week

JAN 17 TO 23

Monday, 18th

UNIVERSITY OF LONDON
5 15 P M (Westminster Medical School, Horseferry Road, S W 1) Prof V M Trikojus (Melbourne) *Aspects of Thyroid Biochemistry*
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P M Mr N W Please *Elements of Statistical Methods*
HUNTERIAN SOCIETY
8 30 P M (Mansion House, E C 4) Prof C Walton Lillehei (Minnesota) *Recent Progress in Open Heart Surgery* (Hunterian lecture)
UNIVERSITY OF ST ANDREWS
4 P M (Queen's College, Dundee) Prof G H Bell *Healing of Fractures*

Tuesday, 19th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Dr John Badenoch *Steatorrhœa in the Adult* (First of two Goulstonian lectures)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr H B Stoner *Biochemical Response to Injury*
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Dr Elizabeth Tylden *Obstetrical Prognosis and Mental Illness*
WEST END HOSPITAL FOR NEUROLOGY AND SURGERY, 91, Dean Street, W 1
5 30 P M Mr Joseph Minton *Ocular Manifestations in Clinical Neurology*
SOUTH WEST LONDON MEDICAL SOCIETY
8.30 P M (Bolingbroke Hospital, S W 11) Mr E H Miles Foxen *Recent Advances in the Relief of Deafness*
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Mr J B Pennybacker *Observations on Trigeminal Neuralgia*
UNIVERSITY OF ST ANDREWS
5 P M (Queen's College, Dundee) Prof Adam Patrick *Encephalitis Lethargica*

Wednesday, 20th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 15 P M *General Practice* Dr Lawrence Dulake, Mr Bryan Brooke, Miss Muriel Powell *Early Ambulation*
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr Hermann Lehmann *What is Thalassæmia?*
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr Henry Haber *Clefts, Vesicles, and Bullæ*
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr N Lloyd Rusby *Sarcoidosis*
UNIVERSITY OF ST ANDREWS
2 30 P M (Queen's College, Dundee) Mr I S Smillie *Physiology of the Knee Joint in Relation to Disease and Injury*

Thursday, 21st

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P M Dr John Badenoch *Steatorrhœa in the Adult* (Second of two Goulstonian lectures)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M Sir George Pickering *Fever and Pyrogens*
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26 Portland Place, W 1
7 30 P M Dr C E Gordon Smith, Mr P F Mattingly, Prof C D Darlington *Arthropod borne Diseases*
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8 15 P M (11, Chandos Street, W 1) Prof Martin Roth *Problems of Mental Health in the Aged*
UNIVERSITY OF ST ANDREWS
5 P M (Queen's College, Dundee) Dr R E Steiner *Radiology and the Portal Circulation*

Friday, 22nd

ROYAL SOCIETY OF MEDICINE
5 P M *Pædiatrics* Prof R A McCance *Development of Acid base Control in the Newly Born* Mr J H Doggart *Eye Changes in Systemic Pædiatric Disease* Dr Giuseppe Pampiglione *Neurophysiological Aspects of Cerebral Ischæmia*
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Mr S O Aylett *Diffuse Ulcerative Colitis with Especial Reference to Treatment by Ileo rectal Anastomosis*
1 P M Mr N W Please *Elements of Statistical Methods*
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
3 30 P M Mr Norman Asherson *Upper Oesophageal Disease*
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W C 1
4 30 P M Dr W H McMenemey *Pathology of Presenile Dementia*

Appointments

BARTON, R W A C, M B Lond, M R C P, D P M physician superintendent, Severalls Hospital, Colchester, Essex
GREVILLE, ELINOR M, M R C S, D P H district M O H, Montgomeryshire (Llanfyllin Montgomery, Welshpool, and Forden districts)
YOUNG, J G, M B Glasg, D P H assistant M O, Dumfriesshire

Birmingham Regional Hospital Board:

ALDERSON, D A, M B, B SC Lond, D M R D part time consultant radiologist, Stafford group of hospitals
BROOKS, WILLIAM, M B Lond, F F A R C S part time consultant anæsthetist *Hereford group of hospitals*
DYSON, M L, M R C S, D M R T, D M R D part time consultant radiologist Wolverhampton and Dudley and Stourbridge groups of hospitals
PARKES, R G F M D Cantab, D P H consultant pathologist, Birmingham (Selly Oak) and Birmingham (sanatoria) groups of hospitals

The Lancet · Saturday 23 January 1960

RESTENOSIS OF THE MITRAL VALVE

AN ACCOUNT OF FIFTY SECOND OPERATIONS

J R Belcher
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ASSISTANT THORACIC SURGEON, MIDDLESEX HOSPITAL, LONDON, W 1

There have been few reports concerning restenosis of the mitral valve, although many second and even third operations must have been performed This paper gives an account of the reexploration of 50 mitral valves

Material

The 50 operations have been done since 1954, and the 12 cases reported in 1958 are included in this number 31 patients had their first operation done by me, and the remaining 19 by other surgeons

The 31 personal cases were from a series of 294 in which the mitral valve had been explored and the patients followed up for more than a year 1 patient from this number has been successfully operated on for a second time in New Zealand.

Incidence

There has been a tendency to use the term " restenosis " only for those cases in which an adequate valvotomy has previously been performed (Bailey and Goldberg 1957, Patterson and Marshall 1959) If this is accepted, another term is required for cases in whom narrowing of the orifice follows an inadequate valvotomy, this narrowing causes deterioration and requires treatment quite as much as that which may follow an adequate valvotomy For this reason, the terms " true " and " false " restenosis are retained (Belcher 1958)

" *True* " *restenosis* was defined as that which might occur when at least one commissure had been fully opened at the first operation In these cases the commissure concerned could often be opened with the finger, and " true " restenosis can be confidently diagnosed when this is so In other cases the assessment at the first operation had sometimes been undoubtedly optimistic, but in all those in which a " good " or " fair-to-good " operation was recorded on the first occasion when restenosis occurred, it has been classed as " true " restenosis

The much commoner " *false* " *restenosis* was defined as that which might follow inadequate commissurotomy In these cases, although considerable improvement often followed enlargement of the orifice, the cusps remained in apposition. As a result the valve orifice was likely to decrease in size again, and so lead to the return of symptoms

Using these definitions, the series comprised 17 examples of " true " restenosis, 29 examples of " false " restenosis, and 4 cases in which no restenosis was found at the second operation Of the personal cases, 17 had had inadequate operations on the first occasion, and therefore had " false " restenosis In the remaining 11, at least one commissure had been fully opened at the first operation, and in some of these it could be readily reopened with the finger these were examples of " true " restenosis (table I)

TABLE I—FINDINGS AT SECOND OPERATION

Restenosis at second operation	First operation		Total
	Personal cases	Other surgeons cases	
" True "	11	6	17
" False "	17	12	29
None	3	1	4
Total	31	19	50

The commissurotomies in the first operations in the personal series were classified as follows those in which both commissures were fully opened as " good " those in which the split was a little less complete as " fair-to-good " those in which only one commissure was fully opened or in which neither was opened completely as " fair " and those in which dilatation only was achieved as " poor " (fig 1)

The incidence of restenosis and of late deaths in each of these groups is shown in table II These totals exclude those patients who died at operation and those in whom exploration revealed dominant mitral incompetence

TABLE II—RESTENOSIS AND LATE DEATHS RELATED TO INITIAL COMMISSUROTOMY

Initial commissurotomy	No	Restenosis	Late deaths
" Good "	86 (*29%*)	0	4 (*5%*)
" Fair-to-good "	135 (*46%*)	7 (*5%*)	7 (*5%*)
" Fair "	61 (*21%*)	16 (*26%*)	5 (*8%*)
" Poor "	12 (*4%*)	8 (*66%*)	2 (*16%*)
Total	294	31 (*11%*)	18 (*6%*)

The incidence of " false " restenosis is only an index of the number of unsatisfactory operations in any given series All save 2 of those who had "poor" operations in the personal series either have had second operations or have died. No commissurotomies in this class have been done since 1955 when the transventricular technique was introduced

Where the valvotomy was thought to have been " fair ", the proportion of patients submitted to second operations has now reached 26% (table II), but fig 2 shows that the longer the follow-up the higher the rate of restenosis has been (table III) the rate amounts to 37% of those operated on more than five years ago It therefore seems likely that the number of patients in this group requiring a second valvotomy will rise as years go by Since the introduction of the transventricular method by

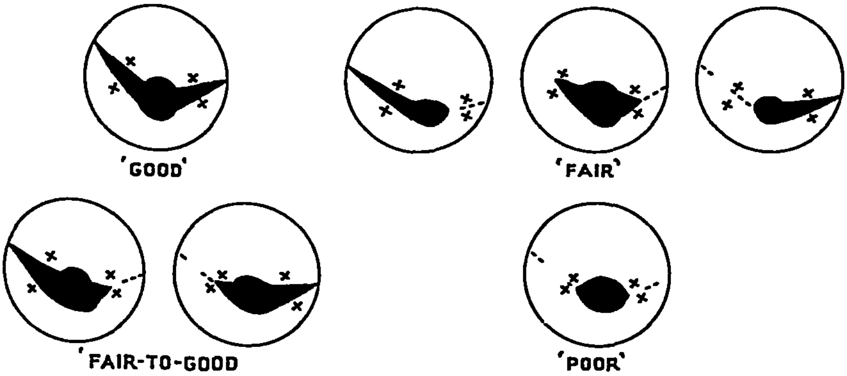

Fig 1—Grade of commissurotomy

TABLE III—NUMBER OF CASES OF RESTENOSIS (R S) RELATED TO NUMBER OF FIRST OPERATIONS, GRADED FROM " POOR " TO " GOOD "

Year	" Poor "		" Fair "		" Fair-to-good "		" Good "	
	No	R.S	No	R S	No	R.S	No	R.S
1952	2	1	5	4	1	0	1	0
1953	4	3	10	4	4	1	7	0
1954	5	4	9	1	30	1	8	0
1955	1	0	8	3	36	4	19	0
1956			9	2	28	1	21	0
1957			15	2	19	0	20	0
1958			6	0	16	0	10	0

Logan (see Logan and Turner 1959) a lower proportion of valvotomies have been considered " fair " in my hands, and it is therefore hoped that the incidence of " false " restenosis will be much less in the future

The incidence of restenosis in the patients in whom the commissurotomy was " fair-to-good " has remained fairly steady at 6–8% (fig 2) This suggests that the mechanism of " true " restenosis may be different from the gradual narrowing of apposed cusps probably responsible for " false " restenosis On the other hand, no second operation has yet been required in my series where the commissurotomy was considered to have been " good " It is therefore still not certain whether " true " and " false " restenosis are different in essence or in degree

It has been suggested that restenosis is due to reactivation of the rheumatic process (McKusick 1955), but no further evidence to support this view has been forthcoming Both Bailey and Goldberg (1957), who had 1 case of restenosis due to reactivation in their first 1000 valvotomies, and Patterson and Marshall (1959) are of the opinion that a cause other than rheumatism must be sought In only 1 of the 50 cases presented here was there any suggestion of reactivation

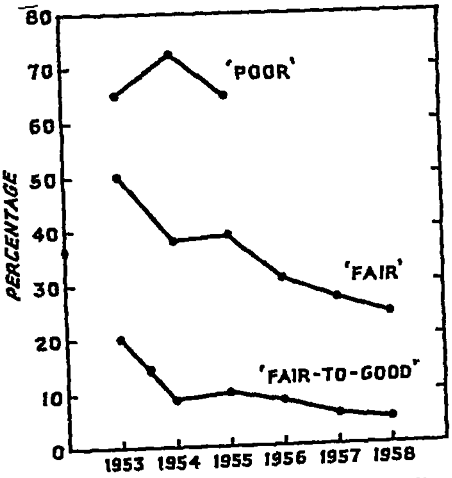

Fig 2—Proportion of patients graded according to results of initial commissurotomy, requiring second operations, by years

Diagnosis

As in cases of primary mitral stenosis, the diagnosis rests on the assessment of the history, of the physical signs, and of special investigations In cases of restenosis, however, more information is available The detailed account of the first operation is all-important, and the postoperative history is often helpful

CLINICAL PRESENTATION

Of the 50 patients 9 were men and 41 were women Their average age was 37 years with extremes of 22 and 51 There appeared to be no difference in the history of those patients with " true " and those with " false " restenosis, except that the average interval between the first operation and the return of exercise tolerance to the preoperative level was shorter in " false " restenosis (25 months as against 34 months)

The return of symptoms, often heralded by " bronchitis ", was usually gradual, but in 9 patients the deterioration was quite sudden, in 4 this sudden reappearance of symptoms could be attributed to the onset of atrial fibrillation, but in others there was no obvious cause (20 of the patients were in sinus rhythm at the time of their original operation, the remainder were fibrillating)

PREOPERATIVE HISTORY

The extent of the improvement achieved by the first operation is important in the diagnosis of restenosis The best guide to the result of any operation for mitral stenosis is the efficacy of the commissurotomy If therefore the first valvotomy was adequate and yet little improvement has resulted, then almost certainly some other factor, such as bronchitis or tricuspid-valve disease, is playing an important part and the diagnosis of restenosis should be made with caution

Secondly, if the degree of stenosis found at the first operation was considerably less than that which might have been predicted from the disability, then again a diagnosis of restenosis may be incorrect, particularly if little improvement was achieved by the first operation

Lastly, if a good result with much improvement in exercise tolerance followed the first operation, and this was followed by deterioration, restenosis is almost certain to be the cause

DESCRIPTION OF FIRST OPERATION

Efficacy of the Split

The most important factor when a second operation is being considered is the description of the first commissurotomy (fig 1) If it was " poor ", a second operation is almost certain to be required eventually If it was " fair "—particularly if neither commissure was opened beyond the critical point of tendon insertion—restenosis is likely If, on the other hand, adequate valvotomy was recorded (" good " or " fair-to-good ") then, if restenosis occurs, it is " true " restenosis, and this is uncommon Other causes of failure must be sought before the diagnosis is made

Mitral Incompetence

In some cases of mitral-valve disease the importance of regurgitation may be difficult or impossible to assess, but, once the valve has been explored, there is less uncertainty if an accurate description of the amount of regurgitation at the end of the first operation is available In the 11 personal cases in this series in which this problem arose, it was found that, although in 3 grade-I incompetence at the end of the first operation had increased to grade-II, and in 3 minor incompetence had appeared, in none had the regurgitation become sufficiently severe to be significant In 1 case grade-I incompetence had apparently disappeared In the remainder the grade of incompetence was unaltered

The increase from grade-I to grade-II incompetence is easily accounted for by error of observation Accurate grading of regurgitation is difficult, particularly when there is some hypotension immediately after valvotomy Grade-I incompetence may also be missed at this time

The grading was done as follows if the reflux was just palpable it was graded as I if it was easily palpable but was not thought to be significant, as II, if severe, as III, if gross as IV (Belcher 1956)

These findings are important, as they suggest that mitral incompetence is unlikely to increase significantly in the years following a valvotomy, and therefore that the description of the regurgitation at the end of the first operation is valuable when the significance of signs of incompetence is being assessed. If little or no regurgitation was reported at the end of the first operation, it is most unlikely to be responsible for symptoms.

Thus the detailed report of the first operation is of paramount importance when a diagnosis of restenosis is being considered.

PHYSICAL SIGNS

Ideally the diastolic murmur is almost abolished by a good valvotomy. Hence were a long loud diastolic murmur to reappear after its abolition by the first operation, a diagnosis of restenosis would be likely. In this series, however, this occurence was recorded only once among the cases of " true " restenosis, and in none of those who had inadequate valvotomies was there a short murmur after their first operation.

The length and character of the diastolic murmur are also unreliable guides, for several patients with tight stenosis had short quiet murmurs, and many patients with long loud ones have excellent exercise tolerance many years after mitral valvotomy. The signs of mitral incompetence (whose importance has already been referred to) must be considered only in combination with the record of the findings at the end of the first operation.

BRONCHITIS

Many patients with mitral-valve disease also have bronchitis, and some of the symptoms of raised left atrial pressure may simulate this condition. Bronchitis may be responsible for the failure of a valvotomy, but, if there is any doubt about the part played by this condition, pulmonary function tests should be done. Capel and Smart (1958) have shown by spirometery that cases in which the bronchitis is the more important factor can be fairly clearly distinguished from those in which the cardiac condition is the major cause of the disability. If the fast expiratory ratio (F.E.R.) is above 65%,

$$\frac{\text{1 sec forced expiratory volume}}{\text{fast vital capacity}} \times 100$$

the heart is almost certainly the organ most seriously affected, but as this figure decreases, obstructive airway disease is more and more likely to be responsible for the dyspnœa, and a second operation is less and less likely to achieve a good result.

RADIOLOGY

Radiographs were found to be of little diagnostic value in cases of restenosis. In many there was little significant change either in the vascular shadows or in the cardiothoracic ratio, despite the return of considerable effort intolerance. The one common feature was the return or the appearance of septal lines. As Grainger and Hearn (1955) have shown that these radiological appearances are due to raised left atrial pressure they are of great diagnostic importance, particularly where no incompetence is present.

OTHER INVESTIGATIONS

Cardiac catheterisation and left atrial puncture were used in a few cases in this series, and were sometimes helpful, but in the majority clinical methods were sufficient to establish the diagnosis.

Second Operation

INDICATIONS

By and large, when restenosis has been diagnosed, the indications for a second operation are the same as those for the first one. Unless there is some contraindication, when a patient's disability returns to the level at which it was before the first operation, reexploration should be undertaken.

The results of the operations in this series show that, although the mortality is a little higher than that of the primary operations, good results can be achieved by a second attack on the valve. This is particularly true when the first one was inadequate. What is perhaps more important is that Ross (1959) has shown that the prognosis in those patients whose first valvotomy has been a failure is surprisingly bad. Among those who died from his series at the Middlesex Hospital, the majority did so within six months of the return of their symptoms to the preoperative level. This being so, once the decision to do a second operation has been taken, the sooner it is done the better.

TECHNIQUE AND FINDINGS

In all cases the approach was through the left atrium. A right-sided approach has been recommended for operations for restenosis (Bailey et al. 1956), because of the difficulties of dissecting the previous operative field, but this has the important disadvantage that it precludes the use of the transventricular dilator which is very often necessary if an adequate split is to be achieved. The dissection, although occasionally tedious, never caused serious difficulties.

In almost all the patients the atrial chamber was reached through an incision in the atrial wall; the appendage had been amputated at the first operation. On several occasions this route had been used already, but the scarring interfered very little with the placing of the purse-string suture on the second occasion. One ring was found to be quite sufficient, but one or two reinforcing sutures were sometimes required to close the atrial wall.

The valve was explored in the usual way. In 22 calcification was present, and both Ross (1959) and Bailey and Goldberg (1957) have referred to the high incidence of calcification in patients requiring a second operation. This is probably a significant finding only in so far as heavy calcification makes valvotomy by the classical method difficult, and its presence was responsible for the inadequacy of the first operation.

In 43 patients it was felt certain that the valve orifice was smaller than it had been at the end of the first operation. In these there was a considerable difference which could not be accounted for by errors of observation. In 3 others it was thought that little alteration had occurred and that the patients had been operated on prematurely, of the remaining 4, 3 had had very inadequate operations on the first occasion and had improved very little, and 1, who died later, had severe mitral incompetence.

Mitral incompetence was present in 21 cases, in 2 it was severe, but the correlation between the severity of the regurgitation recorded at the end of the first operation and that found on the second occasion was close, not only in my cases but also in those treated by other surgeons who had noted this important detail.

After exploration of the valve, finger fracture of the commissures was attempted, but unless this was easily achieved (as it was in 4 of the cases of " true " restenosis) the transventricular approach was used. This procedure almost always gave satisfactory results even when the valve was heavily calcified. The dilatation was done gradually with the blades at right-angles to the direction of the commissures Often two dilators of different sizes had to be used They are so designed that their greatest force is exerted at the end of their range rather than at the beginning, for this reason it was sometimes impossible to start the split with the large dilator, and a small pulmonary or aortic dilator had to be used

Despite careful and gradual dilatation, incompetence was either created or worsened in 20 of the 42 cases in which the dilator was used, in 7 this incompetence was severe Despite the high incidence of incompetence, the transventricular method is at present thought to be that of choice In almost all cases it was possible to achieve a complete commissurotomy, and, as the results show, the incompetence did not prove as serious a complication as might have been expected

Carotid compression was applied during the manipulations, but cerebral emboli occurred in 3 cases (6%) this incidence was higher than that after first operations (Belcher 1956) when it was 2 5% This difference may be due to the high incidence of calcification, with the attendant risk of emboli due to small pieces of calcium broken off the valve edges during the commissurotomy In only 1 patient was the embolus lethal, in the other 2 the effects were transient

RESULTS

Of the 50 patients, 46 have been followed up for more than six months, the longest follow-up period being three and a half years The operative mortality was 8%, compared with 5 5% for the primary valvotomies Of the 4 patients who died, 1 did so from a calcium embolism discovered on X-ray of the brain at necropsy, 2 died from left ventricular failure in the early postoperative period, and 1 died at operation

In the remaining 42 patients the results were as follows

Results	*No*
Excellent	8
Good	17
Fair	10
Poor	4
Late death	3

Thus, over half the patients have a satisfactory increase in exercise tolerance, and in 11 this has been maintained for more than two years Of those who have not done so well, 3 had organic tricuspid-valve disease, and 5 had mitral incompetence, although in only 1 was this thought to be severe In the remainder the cause of the unsatisfactory results are not clear all had adequate commissurotomies

These results are almost as satisfactory as those which might be expected in a similar group of patients after primary operations On this ground alone reexploration of the mitral valves is justifiable The poor expectation of life in patients with restenosis is added justification for a second operation

Conclusions

Probably the number of patients presenting with restenosis of the mitral valve will increase, particularly in the group where the original operation has been inadequate Any patient who has had an increase in exercise tolerance and has thereafter deteriorated must be regarded as a candidate for a second valvotomy A second operation should be undertaken if other causes of failure can be excluded The results of second operations using the transventricular approach justify this policy, and the results of expectant treatment have been shown to be surprisingly bad

Summary

50 operations on account of restenosis of the mitral valve are reviewed

There were 29 cases of "false" restenosis, 17 of "true" restenosis, and 4 in which the size of the orifice had changed little since the first operation

31 of the cases were derived from a personal series of 294 valvotomies followed up for between one and seven years—an incidence of 11%

In the diagnosis of restenosis a detailed report of the first operation is important

The transventricular method of valvotomy has proved advantageous

The operative mortality was only a little higher than that associated with first operations, and the improvement in exercise tolerance was almost as good

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EFFECT OF BEER ON BLOOD FIBRINOLYTIC ACTIVITY

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CONSULTANT PHYSICIAN

John Ferguson
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LATE MEDICAL REGISTRAR

R Chakrabarti
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ALTHOUGH various forms of stress are known to increase blood fibrinolytic activity, only alimentary lipæmia (Grieg 1956) and pregnancy (Biezenski and Moore 1958, Gillman et al 1959) until now have been shown to diminish it Recently we have found that beer may induce profound reduction of fibrinolytic activity in the blood of healthy people During daily observations on a few people an unusual prolongation of blood-clot lysis-time occurred twice, and inquiry revealed a possible connection with the drinking of a glass of beer some three hours before the test This led us to investigate the effect of beer and other alcoholic drinks on blood fibrinolytic activity

Material and Methods

The subjects were healthy people aged 24–45

The method, already described (Fearnley et al 1957), in brief consists in measuring the time required for complete lysis at 37 C of clots made with thrombin of blood diluted 1 10 in phosphate buffer (pH 7 4) A low-temperature technique is essential During the earlier part of the work clot-lysis was judged visually, but following the kind communication by Dr H Lackner of a method of photographic recording (subsequently published by Lackner and Goosen [1959]), an apparatus consisting of a 'Perspex' constant-temperature bath, timing intervalometer, and camera was made for us by Messrs

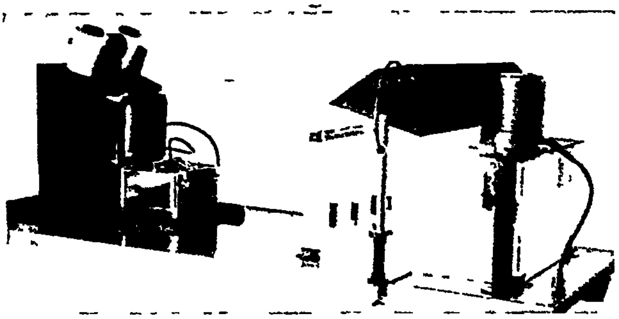

Fig 1—Apparatus for estimating lysis-time photographically

Shackman, of Chesham (fig 1) Photographs were taken at half-hourly intervals on 35 mm. film The film negative is projected, or viewed with a hand lens, to obtain the lysis-times

The Study

Initial Experiments

Two-day experiments were conducted on 2 people (a man and a woman) to test several alcoholic drinks On the first or control day, no alcohol was taken and blood fibrinolytic activity was measured at 5 P M On the second or test day, an alcoholic drink was taken at 2 P M and blood fibrinolytic activity was measured as before at 5 P M Table I shows the results obtained with draught beer, cider, white wine, whisky, gin, and absolute alcohol The lysis-times of both subjects were greatly prolonged on the days on which beer (1 pint and 2 pints), cider, and white wine were taken, but were not significantly altered after gin, whisky, or absolute alcohol were taken The prolongation after ingestion of drinks in the former group was of the order of 300%

TABLE I—VENOUS CLOT LYSIS-TIMES IN A MAN AND A WOMAN ON CONTROL DAYS (NO ALCOHOL) AND ON TEST DAYS (3 HOURS AFTER INGESTION OF DRINKS LISTED)

Drink	Lysis-time (hr)			
	Man		Woman	
	Control	Test	Control	Test
Draught beer, 2 pt.	$4^{3}/_{4}$	$17^{1}/_{4}$	$5^{1}/_{2}$	20
" " 1 pt.	$4^{1}/_{2}$	$13^{1}/_{4}$	5	15
Cider, 1 pt.	5	24	$7^{1}/_{2}$	$19^{1}/_{2}$
White wine, 10 oz.	5	14	$5^{1}/_{2}$	16
Gin, 2 oz	$5^{1}/_{4}$	6	$5^{1}/_{2}$	$6^{1}/_{2}$
Whisky, 2 oz	$6^{1}/_{2}$	$5^{1}/_{2}$	7	6
Absolute alcohol, 2 oz	$5^{1}/_{2}$	$5^{1}/_{2}$	$4^{1}/_{2}$	5

Experiments were then conducted on both subjects to determine the time and duration of the effect of 1 pint of beer Blood was obtained at 2 P M and the beer was drunk in 15 minutes, after which blood specimens were obtained 2, 4, and 6 hours after the first specimen Fig 2 shows that reduction of fibrinolytic activity was greatest at 2 hours, and that in the man the lysis-time had returned to near-resting level at 4 hours, but that in the woman it was still elevated at 4 hours falling to near the resting level at 6 hours

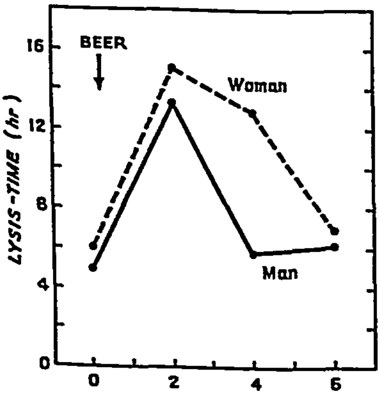

Fig 2—Fibrinolytic activity in relation to ingestion of 1 pint of beer

It thus seemed that consumption jects resulted in reduction of blood fibrinolytic activity which was maximal after 2 hours

Further Experiments

The effect of 1 pint of beer was tested on 14 healthy subjects (10 male and 4 female), blood being tested initially and 2 hours after the beer had been drunk. For convenience bottled beer was used—two well-known brands of fairly high gravity Table II shows the results In 10 of the subjects (nos 1–10) prolongation of lysis-time was pronounced, in 3 subjects (nos 11–13) there was a small and insignificant prolongation, and in 1 subject (no 14) there was no effect whatever

TABLE II—CLOT-LYSIS TIMES OF 14 HEALTHY ADULTS (10 MALE AND 4 FEMALE) BEFORE AND 2 HOURS AFTER DRINKING 1 PINT OF BOTTLED BEER

Subject no	Sex	Lysis-times (hr)	
		Before	After
1	M	2	21
2	M	5	$18^{1}/_{2}$
3	M	4	16
4	M	5	$16^{1}/_{2}$
5	M	7	15
6	M	$3^{1}/$	12
7	F	7	22
8	F	$4^{1}/_{2}$	16
9	F	$5^{3}/_{4}$	15
10	F	6	$15^{1}/_{2}$
11	M	8	10
12	M	4	6
13	M	4	$6^{1}/_{2}$
14	M	$3^{1}/_{2}$	3

Trial of Whisky

To 6 subjects whose lysis-time had been greatly prolonged by beer (nos 1, 2, 4, 5, 8, 9 of table II) 2 oz of whisky, which contained approximately the same amount of alcohol as a pint of beer, was given in 1 pint of water, and the lysis-times were measured initially and after 2 hours Table III shows that whisky in this dosage had no appreciable effect on the blood fibrinolytic activity of any of the subjects

TABLE III—CLOT-LYSIS TIMES OF SUBJECTS 1, 2, 4, 5, 8, 9 OF TABLE II BEFORE AND 2 HOURS AFTER DRINKING WHISKY 2 OZ. IN 1 PINT OF WATER

Subject	Lysis-times (hr)	
	Before	After
1	5	4
2	6	$5^{1}/_{2}$
4	6	7
5	10	9
8	4	6
9	7	8

Trial of Absolute Alcohol

Absolute alcohol in water was given to 3 subjects in a dose of 1 oz and on another occasion 2 oz , and their blood fibrinolytic activity was measured initially and hourly for 3 hours In 1 subject (male) there was moderate prolongation of lysis-time of doubtful significance at 3 hours on the larger dose In another subject (male) there was no significant change In the 3rd subject (female), who was unaccustomed to alcohol, the larger dose produced intoxication and significant quickening of lysis-time from $6^{1}/_{2}$ to $1^{1}/_{4}$ hours at the 2-hour bleeding, after which the experiment was terminated Owing to its unpleasant nature and taste, no further experiments were conducted with absolute alcohol

Discussion

Most, although not all, of the people tested showed a distinct prolongation of lysis-time and hence a reduction of blood fibrinolytic activity after drinking a pint of beer The increases of lysis-time were much greater than we have observed in healthy people given very fatty meals, and it would seem that at any rate in some people beer will induce profound reduction of blood fibrinolytic activity The quantity of beer used was moderate and even small compared with the quantities consumed by some habitual beer drinkers Whisky in a dosage of approximately the same alcohol content as the beer had apparently no effect, the results obtained with absolute alcohol were inconclusive but did not suggest that ethyl alcohol itself was the cause of reduced fibrinolytic activity following beer White wine and cider in two experiments appeared to have an effect comparable to that of beer These results suggest that some substance produced during fermentation and absent from distilled liquors may reduce blood fibrinolytic activity

Most of the people tested were accustomed to alcoholic drink, and 4 of the subjects in table II were asked to participate because they were in the habit of drinking a few pints of beer on one or more nights of the week In only 1 of these 4 (no 12) was there no significant alteration of lysis-time It does not seem, therefore, that reduction of blood fibrinolytic activity by beer is likely to cease with habituation

Until blood fibrinolytic activity has been proved to be of functional importance—which as yet it has not—it would be premature to speculate about the possible significance of these findings, and they do not in our view justify any further restriction on sufferers from vascular disease Their importance, however, to people who are measuring blood fibrinolytic activity is obvious

Summary

Preliminary experiments on 2 people indicated that draught beer, cider, and white wine greatly lowered blood fibrinolytic activity, whereas whisky, gin, and absolute alcohol did not

In 10 out of 14 people the ingestion of 1 pint of bottled beer was followed by pronounced lowering of blood fibrinolytic activity 2 hours later, in the remainder no significant change occurred

In 6 of the subjects who showed a response to beer, whisky in a dose of 2 oz had no significant effect on blood fibrinolytic activity

Absolute alcohol in 3 subjects yielded inconclusive results, but the evidence suggests that some fermentation product other than ethyl alcohol was responsible for the change in blood fibrinolytic activity which followed the drinking of beer

We wish to thank Messrs G D Searle & Co , Ltd , for their generous grant which defrayed the cost of the apparatus, Dr G R. Venning, their medical director in England, for his great help and interest, Dr Edgar Davey for kindly giving us laboratory facilities, and our volunteers, who prefer to be unnamed

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LIPÆMIA AND FIBRINOLYTIC POTENTIALITY *

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Macfarlane (1937) was the first to demonstrate spontaneous fibrinolysis in the blood of patients after surgical operation With Biggs and Pilling he later found fibrinolytic activity in the blood of healthy volunteers after exercise or the injection of adrenaline (Biggs, Macfarlane, and Pilling 1947) In the technique used by these workers, the test plasma was diluted with a buffer and clotted by addition of thrombin, the rate of disappearance of the fibrin clots was then determined Fearnley, Revell, and Tweed in 1952 showed that if the plasma was kept chilled until the test was set up, fibrinolysis of varying degree could be demonstrated in healthy people even at rest

The rate at which the clot dissolves or lyses depends not only on physical factors, such as ionic strength and hydrogen-ion concentration, but also on the balance of inhibitors and activators in the diluted plasma For example, a decrease in an inhibitor without any change in the concentration of activators would enhance lysis Celander and Guest (1958) therefore proposed that the activity measured by such a dilution system be called the *fibrinolytic potentiality* of plasma This term emphasises that the test system does not measure merely plasmin (syn , fibrinolysin) which is believed to be the enzyme directly responsible for the breakdown of fibrin

Greig (1956) and Greig and Runde (1957) found that the lipæmia following a fatty meal significantly inhibited fibrinolytic activity Greig and Runde also found that the fibrinolytic activity of blood tends to be lower in people with a high serum-cholesterol level than in those with a lower level

There is evidence that platelets inhibit the action of plasmin (Johnson and Schneider 1953, Hume 1958), and they might therefore be expected to inhibit fibrinolytic potentiality But, so far as we know, this possibility has not been examined As cephalin can replace platelets in several coagulation test systems we thought that cephalin and platelets might have similar actions on fibrinolytic potentiality

The present work includes an attempt to answer these questions

Material and Methods

After trials of the method of Greig (1956), the method of Fearnley and Lackner (1955), a later modification of this method by Fearnley et al (1957) and several of our own modifications, all these were abandoned in favour of the method published in outline by Celander and Guest (1958), which was chosen as giving the greatest precision and the most reproducible results Our modifications and unpublished details of this method (Guest 1958) are

3 5 ml blood, collected into glass vacuum tubes, were mixed immediately with 1 0 ml of 3 8% trisodium citrate and 0 5 ml of 0 089 *M* KH_2PO_4 in a graduated siliconed centrifuge tube This blood was centrifuged (see below for details) and 0 3 ml portions of plasma were added to a number of tubes, each containing 5·0 ml phosphate buffer (pH 6 4), 0 2 ml thrombin (50 units per ml) and

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*This investigation was supported by Grant H 3536 from the National Heart Institute, National Institutes of Health, Public Health Service, U S.A a glass rod After the contents had been vigorously mixed, these tubes were kept in an ice-bath for thirty minutes The clots which formed were then immediately removed from the tubes by slowly turning the glass rods until all particles of the clots firmly adhered to their surface. They were then "washed" by dipping them into another container holding more of this same buffer (pH 6·4) All reagents, material, and equipment, including blood, were kept ice-cold from the beginning of the experiment until after this clotting period

Initial estimation of fibrinogen was made from at least two clots, each dissolved in 1 ml *N* NaOH immediately after the thirty-minute period of clot formation Percentage lysis was determined from four clots, two of which had been left to lyse for exactly thirty minutes and the other two for sixty minutes, each in 5 ml phosphate buffer (pH 7 7), and then dissolved in NaOH. For the colorimetric procedure Lowry's modification of the Folin-Ciocalteu method was used

The standard deviation (S D) of our technique was calculated from a series of 20 duplicate results by a method described by Youden (1951) and was ±4 8% in terms of percentage lysis in one hour

TABLE I—COMPARISON OF FIBRINOLYTIC POTENTIALITY OF PLATELET-POOR AND PLATELET-RICH PLASMA

Experiment	% lysis	
	Platelet-poor plasma	Platelet-rich plasma
1	57	21
2	30·4	23
3	29	13
4	31	13
5	38	30
6	100	70
7	27	25
8	31	30
9	25	23 5
10	17	8

To determine the effect of platelets on the test system, the patient's blood (which was kept chilled) was placed in two identical 'Lusteroid' containers One of these was centrifuged for seven minutes at 1500 r p.m (approximately 500 *g*) The other was spun at 15,000 r p.m. (approximately 15,000 *g*) for five minutes so as to sediment the platelets This latter specimen is referred to as platelet-poor plasma and the former as platelet-rich plasma.

Washed platelets in suspension were prepared by the method of Biggs and Douglas (1953) They were used in a test within four hours of the time the blood for their preparation was drawn.

Control tubes run in each experiment contained an amount of 0 85% saline equal in volume to the material being tested (i.e., cephalin or washed platelets)

Results

Comparison of fibrinolytic potentiality of platelet-rich and platelet-poor plasma—Platelet-rich and platelet-poor plasma was obtained from each of 10 normal subjects and the lysis-rates were compared Table I shows that after one hour there was more lysis in the platelet-poor plasma than in the platelet-rich plasma The difference is significant at the 1% level

TABLE II—EFFECT OF ADDITION OF WASHED PLATELETS TO PLATELET-POOR PLASMA

Experiment	% lysis	
	Saline control	Washed platelets
1	55	48·6
2	38	21
3	34	25 5
4	50·6	49 8
5	36·5	40·6
6	66	47 8
7	62	59 7
8	43	45
9	91	44·9
10	33	26
11	19 8	20
12	20·6	16·9
13	17	13
14	47	47 5
15	30·5	25

TABLE III—EFFECT OF ADDITION OF CEPHALIN TO PLATELET-POOR PLASMA

Experiment	% lysis	
	Saline control	Cephalin
1	31 7	20
2	28	28
3	15	25
4	23	26
5	34	35
6	27	25
7	24	32
8	20	22
9	63	64

Effect of addition of washed platelets to platelet-poor plasma—Table II shows that the twice-washed platelets inhibited fibrinolytic potentiality, but the level of significance was lower (5% level) than in the previous experiment.

Effect of addition of cephalin to platelet-poor plasma—Cephalin prepared by the method of Bell and Alton (1954) and added to platelet-poor plasma was found (table III) to have no statistically significant effect on lysis in our test system

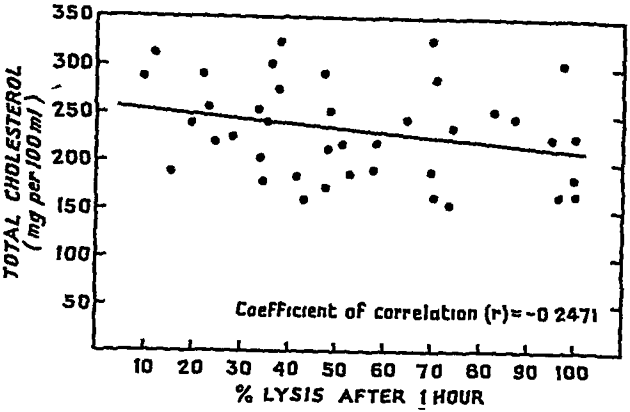
Effect of fatty and non-fatty meal on fibrinolytic potentiality of plasma—This experiment was carried out on 9 healthy males The fatty breakfast consisted of bacon, eggs, toast, a very large serving of butter, and at least one glass of cream, while the regular breakfast consisted of coffee-with-milk, fruit juice, and a dry bread roll The meals were taken between 7 30 and 8 0 A.M and the blood was drawn three and a half to four hours later Care was taken to ensure that after the fatty and regular breakfasts the subject went through the same daily routine.

The results (table IV) show no statistically significant difference in lysis after the fatty and the non-fatty meals, using either the half-hour or one-hour determinations

TABLE IV—LYSIS AFTER FATTY AND NON-FATTY MEALS

Experiment	% lysis after half an hour		% lysis after one hour	
	Regular meal	Fatty meal	Regular meal	Fatty meal
1	32 39	33 33	33 91	40·00
2	45 19	50·00	100 00	100·00
3	17·45	32 15	40 78	41 32
4	38·02	29·09	47 53	45·45
5	37 32	30 16	58 61	70 75
6	82·42	39·03	100·00	82·91
7	10·47	27 11	24 42	46·45
8	35·07	29 24	87 76	82 12
9	38 32	29·94	97 29	100·00

Relation of serum-cholesterol level on fibrinolytic potentiality of plasma—The subjects in this experiment were 40 normal people (28 males and 12 females) ranging in age from 15 to 60 Blood was drawn from 25 of them between 9 00 and 11 00 A.M (in most cases at about 10 00) and from the remaining 15 patients between 1 30 and 2.30 P.M (usually at 2 00) Although there is a normal diurnal fluctuation in lysis-rate (Fearnley et al 1957, Buckell and Elliott 1959a), there is also significant fluctuation from day to day even though blood is drawn at the same time of day and the person has taken the same food and done the same work Because of the large number of cases studied, we felt that variations of the type mentioned would be relatively unimportant The percentage lysis was determined after both thirty and sixty minutes There was no significant correlation between cholesterol level and fibrinolytic potentiality, either after sixty minutes' (see figure) or thirty minutes' lysis



Correlation of total cholesterol and percentage lysis with line of regression for all plotted points

Coefficient of correlation is −0 2471 To be significant even at the 0 05 level, this figure would have to be numerically greater than 0 304

Discussion

Our finding that a fatty breakfast did not significantly inhibit fibrinolytic potentiality is in striking contrast to Greig's finding of inhibition in all his 25 subjects Buckell and Elliott (1959a and b), using a method similar to Greig's, claimed to have confirmed his finding of significant inhibition of lysis following a fatty meal—at least in subjects aged 20–24 This conclusion, however, is not supported by inspection of their actual data (see table I, Buckell and Elliott 1959b), for the rate of lysis was decreased in only 8 of their 20 cases when determined after six hours and in 5 out of 20 when determined after twenty-four hours Nitzberg et al (1959) using the dilution method of Fearnley et al (1957), studied three groups of subjects 9 patients with idiopathic hyperlipæmia, 10 patients with primary hypercholesterolæmia, and 10 normal people In all but 3 of these 29 they found actual enhancement of fibrinolytic potentiality but they regard these results as inconclusive because of the limitations of the method We, too, have used this method, but abandoned it because we could not obtain precise or reproducible results Billimoria et al (1959) demonstrated a significant inhibition of lysis two hours after a fatty meal but found no significant inhibition of lysis four hours after a fatty meal, this latter finding is in accord with our results

As emphasised earlier, dilution methods which measure fibrinolytic potentiality do not necessarily measure plasmin, so our data do not exclude the possibility that fats inhibit plasmin It is interesting to note, however, that Buckell and Elliott (1959b), using a euglobulin lysis-time method, could find no significant difference in lysis-times after fatty and non-fatty meals This is a more specific method of measuring plasmin, since most inhibitors are removed during the euglobulin precipitation However, Mandel (1959), using a method which employs streptokinase activation and a visual endpoint has found delay of lysis in plasma after addition of fat, both in vitro and vivo He found that 'Lipomul' (peanut oil with dextrose) caused marked inhibition, whereas cream caused only moderate inhibition, and 'Arcofac' (containing linoleic acid) caused none Nitzberg et al also used a method involving streptokinase activation, and their results were similar to those of Mandel With this method (in contrast to their results with the dilution method) the majority of subjects showed some prolongation of lysis-times after a fatty meal

We were unable to confirm Greig and Runde's finding of a significant inverse correlation between level of cholesterol and fibrinolytic potentiality We have recently determined the fibrinolytic potentiality of a patient with familial hypercholesterolæmia (total serum-cholesterol 824 mg per 100 ml) Even though blood was drawn at 11 00 A M , when lysis-rate should be slower than in the early afternoon, the patient's fibrinolytic potentiality exceeded that of 23 of our series of 40 people whose blood was drawn either at this time or early in the afternoon. This result indicates that the increased tendency to coronary disease in this condition may not necessarily be associated with diminished fibrinolytic potentiality

Summary

When a dilution test system is used, fibrinolytic activity is inhibited in platelet-rich plasma, as compared to platelet-poor plasma Cephalin appears to have no effect on fibrinolytic activity

We were unable to confirm the finding of others that lipæmia inhibits fibrinolytic potentiality Our results indicate that ingestion of butter, cream, and eggs has no significant effect on fibrinolytic potentiality determined between three and a half and four hours after the meal There was no significant correlation between fibrinolytic potentiality and the level of total cholesterol in the serum

We wish to thank Dr Richard Shaw of the department of preventive medicine, University of Virginia, for help with the statistics

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TREATMENT OF WILSON'S DISEASE WITH PENICILLAMINE

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Patients with Wilson's disease are in positive copper balance (Cartwright et al 1954, Zimdahl et al 1954), and, as a result, copper accumulates in the tissues, principally the brain, liver, and kidneys, and is excreted in excess in the urine Deposition of copper in these organs is associated with degenerative changes, in the brain affecting most often the basal ganglia and leading to the tremor-rigidity syndrome, in the liver leading to cirrhosis, and in the kidneys leading to abnormalities of renal tubular function which in turn gives rise to glycosuria, amino-aciduria, phosphaturia, and uricosuria of the "low threshold" type. Deposition of copper in Descemet's membrane of the cornea is responsible for the development of the characteristic greenish-brown Kayser-Fleischer rings.

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Up to 1948 Wilson's disease was considered to be without treatment. In that year, however, Cumings pointed out that dimercaprol (BAL), by removing copper from the tissues, should be of benefit to patients with this condition. Subsequently there have been many reports on the therapeutic efficacy of dimercaprol, and most workers have agreed that it has a real, if limited, use in the management of Wilson's disease (Cumings 1948, Denny-Brown and Porter 1951, Bearn 1956), although in some series little benefit has been observed (Bickel et al 1957). One difficulty in understanding the response to dimercaprol has been the very poor correlation between the clinical and biochemical results leading some workers to wonder whether removal of copper from the tissues was as important as had been originally supposed (Bearn 1957, Uzman 1958, Walshe 1959). The introduction and trial of other therapeutic agents clearly testifies that dimercaprol is not the final answer to the treatment of Wilson's disease. Of these newer compounds penicillamine (ββ dimethyl cysteine) is the latest, and this is, in the majority of cases, the most powerful "decoppering" agent (Walshe 1956, Bearn 1957).

Hitherto no large series of patients treated with penicillamine has been published, so its clinical usefulness cannot yet be assessed. We have collected data on 22 cases treated with this compound, recorded its cupriuretic action, its therapeutic effect, and, where possible, compared these with the corresponding actions of dimercaprol.

This report is not the result of a planned therapeutic trial. The results have been collected post hoc and are, therefore, lacking in certain details.

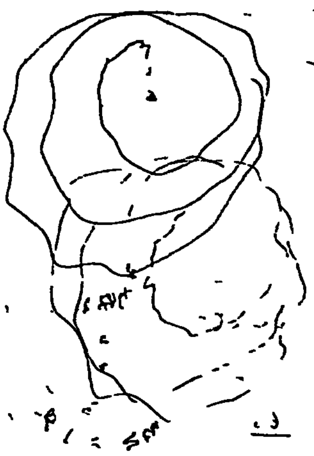


Fig 1—Case 19 spiral and attempted signature before treatment with penicillamine.

Clinical Material and Methods

This report concerns 22 cases with Wilson's disease collected from sixteen hospitals (12 patients in England, 5 in Scotland, 2 in Canada, 1 in Northern Ireland, 1 in Germany, and 1 in Israel).

The average age at onset was 14·8 years, the youngest presented at the age of 8 years with hepatic enlargement and the oldest at 32 years with tremor (a patient who presented with cirrhosis at the age of 11 years had had an attack of "jaundice" at the age of 3 years) (table I).

The dosage of penicillamine (D-penicillamine hydrochloride, Distillers Company (Biochemicals) Ltd.) varied from 500 mg to 3 g daily, most patients receiving 900 mg or 1 g a day. The

TABLE I—CLINICAL DATA

Case no	Age (yr)	Sex	Presenting symptom	Length of illness (mos)	Serum-Cu (µg per 100 ml)	Serum-oxidase activity	Urine Cu (µg per 24 hr)	Remarks
1	23	F	Choreoathetosis	60		0·085	172	Advanced case with decorticate rigidity when first seen
2	12	F	Unsteady gait	42		Very low	540	Patient suddenly deteriorated and died in hepatic coma
3	37	M	Tremor	60	80	0·07	180	
4	13	F	Parkinsonism, spontaneous movements	9	50	Low	400	Biochemical diagnosis, aet. 9, symptoms aet 12
5	21	M	Cirrhosis of liver	120	46	Low *	84	Published Warnock and Neill (1958). Hepatic case with no C.N.S. involvement
6	11	M	Hepatomegaly	36	120	Normal	160	Hepatic case with no C.N.S. involvement
7	22	M	Coarse tremor arms	12	60	0·01	395	
8	20	M	Parkinsonism	84		Very low	500	Published Fister et al (1958), case 2
9	24	F	Tremor	18		Very low	275	To be published Boag and Boulding (1960)
10	23	M	Tremor of hands	60	50–80	Low	500	
11	16	F	Tremor of hands	36		0·14	490	
12	21	M	Difficulty in walking	84		0·01	200–400	
13	18	M	Slurred speech, choreiform motions	60	50	0	540–880	
14	13	F	Jaundice	36	131	0·06	340–780	
15	13	F	Jaundice and ascites	29	93	Normal	200–400	Cæruloplasmin normal by fractionation and enzymatic methods
16	12	F	Choreiform syndrome	12		0·05	236–334	Also showed much emotional instability
17	27	M	Intention tremor	48	40–50		400–800	Published Lange (1958), case K. D.
18	17	F	Intention tremor	96	52		200	Also much emotional disturbances
19	19	F	Parkinsonism—salivation	72	50	0	370–480	Published Walshe (1956), case 3, Osborn and Walshe (1958), case 1
20	20	M	Dysarthria ataxia	60	41	0	300–500	Published Osborn and Walshe (1958), case 3
21	21	M	Renal rickets	60	35–43	Very low	400–600	C.N.S. signs developed 2 yr after onset of rickets
22	26	F	Tremor and Parkinsonism	60				Kayser-Fleischer rings and œsophageal varices present

* =9·4 mg per 100 ml as cæruloplasmin

duration of treatment varied from four weeks to three years with an average of one year

16 of these patients received dimercaprol, either alone or in combination with penicillamine In most cases it was given in short courses of five days or a week, either every ten days or once a month Often a single weekly maintenance dose was also given The largest dose was 400 mg daily, the smallest 50 mg to a 12-year-old child

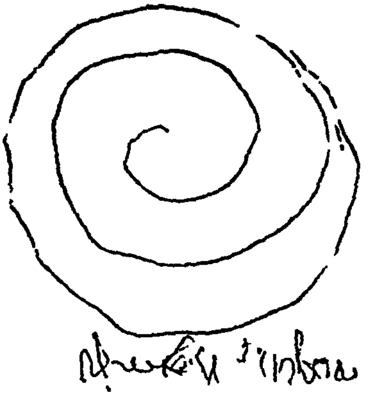


Fig 2—Case 19 improvement in spiral and signature after start of therapy

No attempt has been made to report on chemical methods as the results have been collected from so many laboratories Cæruloplasmin was, in most cases, estimated as units of oxidase activity, according to Ravin (1956), though in other cases the content was recorded as " low " or " very low " (presumably as Ravin units)

No one physician saw all the patients, and in any case assessment of clinical improvement is apt to be subjective, but, in our experience, it is usually obvious when benefit follows treatment Benefit has been recorded only when a patient became able to undertake tasks which were previously impossible, such as feeding or dressing himself One of the best measures of improvement is by keeping records of handwriting and ability to draw a spiral (figs 1–4), but unfortunately such records are available in only a few of our cases

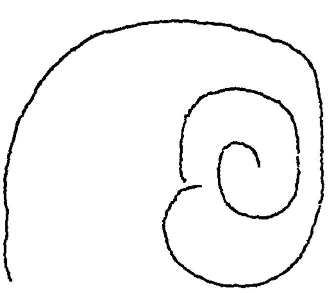


Fig 3—Case 19 further improvement in performance after 2 years treatment

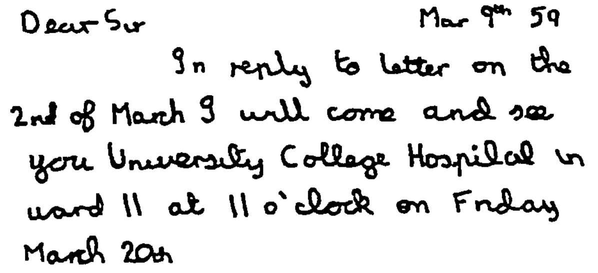
Results

Details of the results are shown in table II Of the 22 patients 2 (cases 5 and 6) were found to have the bio-

TABLE II—RESULTS OF TREATMENT

Case no	Dimercaprol			Penicillamine		
	Duration and dosage	Maximum urine Cu (µg per 24 hr)	Clinical response	Duration and dosage	Maximum urine Cu (µg per 24 hr)	Clinical response
1	Intermittent courses, 18 mos	Incontinent	Doubtful improvement, remained incontinent	1 month 1 g daily, later 3–4 g daily	1286	Delayed response but ' spectacular effect '—much improved
2	10 days 50 mg daily	570	No response	10 weeks 1 g daily	1680	No response
3	Only given with penicillamine		No response	5 mos 1 5 g daily	3800	No response
4	14 days 100 mg daily		No response	6 mos 0·9–1 2 g daily	2330	No response—deteriorated Jacksonian epilepsy
5	7 yr courses each 3 mos	2835	Liver tests improved	3 yr 1 5 g bi-weekly	2200	No symptoms—remains well
6	14 days 80 mg daily	137	Given after penicillamine	2 mos 0 5 g daily	1340	No symptoms—remains well
7	Only with penicillamine	1450		4 mos 0 9 g. daily	2550	Significant reduction of tremor
8	Monthly courses 3 mg per kg daily	2714	Temporary improvement only	2 yr 0·9 g daily	4524	From being bedridden has returned to school
9	Nil			15 mos 0 9 g daily	6250	From being helpless can now feed and dress herself and is nearing full term pregnancy*
10	7 day courses for several mos , 400 mg daily	1350	Deteriorated	15 mos 0·9 g daily	3600	Disappearance of all symptoms
11	Nil			9 mos 0 9 g daily	2000	From being helpless is now symptom free and successful wage-earner
12	3 days only, 200 mg daily	1000		22 mos 1·0 g daily	2500	Improved gait and speech Virtual loss of K-F rings
13	14 days 150 mg daily	900	No response	1 yr 0 9 g daily	3360	Choreiform motions and limb motions much improved, slurred speech
14	Nil			15 mos 0 9 g daily		Very good—returned to full activities at school
15	Nil			13 mos 0 6 g daily	2380	Moderate improvement
16	Nil			12 mos 0·9 g daily	2270	All symptoms disappeared, normal school activities
17	2 courses, first total 5 6 g , second total 6 3 g	990	Improved	2 courses 2 mos and 4 mos 0·9 g daily	3428	Intention tremor improved Relapse 3 mos after treatment stopped
18	Courses of 1 week each	720	Initial improvement —not found with later courses of treatment	7 mos 0·9 g daily	400	Continued improvement—almost symptom-free Virtual disappearance K F rings
19	3 courses 5 days 100 mg daily	600	Decreased rigidity	2 yr 0·9 g daily, 1 yr 0 45 g daily	3000	From being dysarthric and bedridden to full activities
20	8 weeks 70 mg daily	800	Febrile reaction Discontinued	2 yr 0·9 g daily	1200 (6 hr)	Much improved can now feed, shave and dress himself
21	Nil			1 month 0·9 g daily	2100 (6 hr)	Improved writing, can now feed himself
22	5 days, 400 mg daily	1640	No response	8 mos 0·9 g daily	750	Much objective improvement in rigidity and tremor

* Subsequently delivered a normal full term child



Dear Sir Mar 9th 59

In reply to letter on the 2nd of March I will come and see you University College Hospital in ward 11 at 11 o'clock on Friday March 20th

Fig 4—Case 19 clear and legible writing after 3 years on continuous penicillamine

chemical stigmata of the disease after the condition had been diagnosed in an elder sibling

Both these patients were found to have hepatomegaly, but, up to the time of writing, there was no evidence that the central nervous system was involved although Kayser-Fleischer rings were present. Neither of these patients deteriorated on maintenance therapy 1 (case 5) showed a better cupruretic response to dimercaprol than to penicillamine, but as he had been under treatment for four years before the introduction of penicillamine the comparison may not be valid. The other (case 6) had no increased excretion of copper after receiving dimercaprol, but this was given after two months on penicillamine.

3 patients (cases 2–4) either did not improve or actually deteriorated under treatment, and 1 of these died from hepatic failure All 3 showed an excellent cupruretic response to penicillamine, though there is no evidence that they were in negative copper balance All were also treated with short courses of dimercaprol and similarly showed no improvement

TABLE III—SUMMARY OF TREATMENT RESULTS

Drug	Greatly improved	Limited improvement	No benefit	Prophylaxis	Toxicity	Not assessed
Penicillamine	6	11	3	2	1	0
Dimercaprol	1	2+1*	4	2	1	5

* Limited improvement, later deteriorated on treatment

17 cases remain in which the degree of benefit varied from "choreiform movements and control of limbs much improved but speech still slurred" to complete recovery so that, after being bedridden and helpless, they returned to full activity and have become symptom-free In 11 cases there was a good, but limited, response (cases 1, 7, 9, 12, 13, 15, 17, 18, 20–22), but 4 of these have so far received less than a year's treatment with penicillamine, and 1 (case 21) has been under treatment for only one month at the time of writing but already appears to be responding well Finally, 6 patients who were severely incapacitated and bedridden at the start of treatment with penicillamine were able to return to a normal degree of activity (cases 8, 10, 11, 14, 16, 19), and those who had shown signs of mental instability also improved in this respect In 2 patients significant fading of the Kayser-Fleischer rings was observed during the period of penicillamine therapy Of the 16 patients treated with dimercaprol 2 (already mentioned) were in the presymptomatic stage of the disease (cases 5 and 6), but only 1 of these had a good cupruresis after receiving the drug Of the remaining 14 patients, 1 improved greatly and 3 to a limited extent, but all had a poor cupruresis (cases 1, 17–19) Later all received penicillamine and continued to improve, 1 (case 19) falling into the group of "excellent response" 1 patient had a severe febrile reaction to dimercaprol, which was discontinued, and another refused further treatment because of pain at the injection sites (cases 20 and 18) 1 patient (case 8) had a good response to his initial treatment with dimercaprol, but then deteriorated despite adequate maintenance therapy He later had an excellent response to penicillamine, and this applied also to case 10 who on dimercaprol had gone downhill steadily 2 patients (cases 3 and 7) received dimercaprol only in combination with penicillamine The remainder (cases 2, 4, 12, 13, 22) were all treated for less than a month with dimercaprol, and their failure to respond does not necessarily mean the drug would not have been effective if therapy had been prolonged, but only 1 of these (case 22) had a good cupruresis following administration of dimercaprol (table III)

There was one serious toxic reaction to the D isomer of penicillamine, case 4 developing an erythematous rash and jacksonian convulsions There was, however, no other evidence of any anti-pyridoxine activity (as reported by Kuchinskas and du Vigneaud [1957] for L-penicillamine) or of depletion of other trace metals 2 patients developed transitory rashes which did not necessitate discontinuance of therapy although 1 of these required the simultaneous administration of an anti-histamine drug to control the rash

Discussion

While these results leave little room for doubt that penicillamine is of value in the treatment of Wilson's disease, they still do not answer the question Is the removal of copper from the body the mode of action of chelating agents? The alternative suggestion has been put forward that they may operate by providing sulphydryl groups for intermediary metabolism (Walshe 1959, Hill and Walshe 1959) In most cases in the present series penicillamine proved more active than dimercaprol, both in mobilising copper and in promoting clinical improvement, but 3 cases, despite satisfactory cupruresis showed no improvement or actually deteriorated This lack of correlation between biochemical and clinical findings remains one of the big unsolved problems of this disease. What is the essential difference between patients who respond and those who do not? How can one predict in advance into which group any given patient will fall? Certainly the clinical condition of the patient when first seen and the initial cupruresis give no evidence on which to base prognosis As it costs approximately £1 a day to treat a patient with penicillamine, it would clearly be advantageous to know in advance whether any benefit will accrue, but it is still cheaper to treat a patient at home with this drug than to allow him to become bedridden and require hospital care, so (apart from other considerations) expense should not limit the use of penicillamine.

In this study no attempt has been made to determine the minimum dose or to establish whether this can later be reduced for maintenance therapy, but in 3 patients (cases 10, 11, and 17) minimum effective therapeutic doses were established as 0 6, 0 9, and 0 9 g daily respectively Similarly, no mention has been made of the use of potassium-sulphide and low-copper diets to limit absorption of metal from the gut, although both measures should be employed Finally, the rate at which a patient will respond to treatment has not been discussed With dimercaprol any improvement generally occurs early, though it is not always maintained and later the patient ıay deteriorate on maintenance therapy With penicill-mine the response appears to be slower, but when it ccurs it is often continuous over several years so that the atient will eventually return to normal or near-normal lthough a relative biochemical resistance to the drug may evelop The mechanism of such resistance and the min-num maintenance dosage have yet to be determined : will certainly be of advantage if others who may be ndertaking the treatment of patients with Wilson's isease would join in a further scheme to evaluate the fficacy of various treatment schedules The plan of ımpaign should be carefully drawn up in advance

Summary

A collected series of 22 cases of Wilson's disease treated ith penicillamine has been studied 16 of these patients so received dimercaprol either alone or synchronously ith penicillamine

Of the 22 patients 3 showed no response, 11 showed nited improvement, and 6 became symptom-free, the maining 2 were given penicillamine prophylactically :fore clinical evidence of neurological involvement ıpeared

Of the 16 patients treated with dimercaprol, 1 improved ıtably and 3 to a limited extent but 1 showed only tem-ırary improvement, 4 did not respond, 2 were in the esymptomatic stage of the disease, and 5 received adequate amounts of dimercaprol to draw conclusions

1 patient treated with dimercaprol had a severe febrile action necessitating cessation of treatment 2 patients ı penicillamine had mild transitory rashes which gave ıe to no inconvenience, 1 patient developed jacksonian ılepsy on this treatment

[thank Dr Michael Ashby, Dr H G Morgan, Dr S Nevin, and W C Smallwood for allowing me to study their patients, and C N Brown, of the Distillers Company (Biochemical) Ltd , for ıerous gifts of D-penicillamine hydrochloride

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' Fundamentally the society in which we live does not e sufficiently about the dangers to which its members will exposed when they enter the surgical part of its hospitals give us the means we require in order to employ to the lest extent the knowledge we already have about the vention of infection, and to search with all our power for further knowledge we need In 1965 it will be one ıdred years since Lister first pointed the way toward the dication of infection from surgical hospitals Shall we, successors, be able to celebrate this event with a clear, ıpy consciousness of having worked as hard as he did to ıe his dream come true?"—Prof G J FRAENKEL, *The ımple of Joseph Lister*, an inaugural lecture, p 10 (Dunedin ıversity of Otago Press 1959 2s 6d)

EFFECT OF CORTICOSTEROIDS AND GLUTEN-FREE DIET ON ABSORPTION OF IRON IN IDIOPATHIC STEATORRHŒA AND CŒLIAC DISEASE*

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IN idiopathic steatorrhœa and cœliac disease iron is absorbed very poorly, even in the presence of gross iron deficiency, and conventional treatment with a high-protein, low-fat diet and vitamin and mineral supplements does not improve the absorption of iron (Badenoch and Callender 1954)

Recently, corticosteroids and the gluten-free diet have been introduced for the treatment of these conditions, and, in contrast to earlier forms of therapy, both have been shown to improve the absorption of fat and other substances (Taylor et al 1952, Anderson et al 1952) From the rise in hæmoglobin which sometimes occurs with either form of therapy it has been assumed that iron absorption is also improved, but no direct evidence for this has been reported

In this study we have measured the effect of treatment with corticosteroids and gluten-free diet on iron absorption in patients with idiopathic steatorrhœa and cœliac disease and in control subjects, using radioactive iron as a tracer

Material and Methods

Ten patients with idiopathic steatorrhœa or cœliac disease were investigated The majority had been receiving treatment with a high-protein, low-fat diet and vitamin and mineral supplements, including folic acid, vitamin B_{12}, and iron, for several years As a result few were anæmic, but most of the blood-films showed evidence of iron deficiency and six of the ten had a serum iron of less than 50 μg per 100 ml

The controls were twelve patients without anæmia or disease of the gastrointestinal tract

An oral dose of 5 mg of iron labelled with 4–5 μC of ^{59}Fe was given to each patient as a solution of ferrous sulphate to which 25 mg of ascorbic acid had been added to ensure that the iron remained in a reduced form The dose was given while the subjects were fasting, and they received nothing by mouth for a further two hours

Throughout we have used the maximum radioactivity appearing subsequently in the blood as a measure of the absorption of iron, although in a few instances the unabsorbed radioactive iron in the fæces has also been measured It is well recognised that in iron-deficient subjects the proportion of the oral dose of iron which appears in the red cells is a good index of the amount absorbed In non-anæmic subjects it may represent only some 70–100% of that actually absorbed, but as we had evidence that steroids, given under the conditions of these experiments, do not alter significantly the percentage of the iron utilised (unpublished observations), we felt that for comparative studies before and after treatment the blood-levels alone were sufficient. The maximum radioactivity in the blood was usually reached 10–15 days after the oral dose Activity was measured in 10 ml samples of blood and compared with that of a standard prepared from the individual oral dose (Badenoch and Callender 1954)

With the exception of one subject, who had been taking cortisone in a dose of 20–100 mg daily for 12 months prior to the test, steroids were administered to both patients and controls, either in the form of prednisone 40 mg daily for 5–6

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* Based on a paper given at the Seventh International Congress of Hæmatology, Rome, 1958

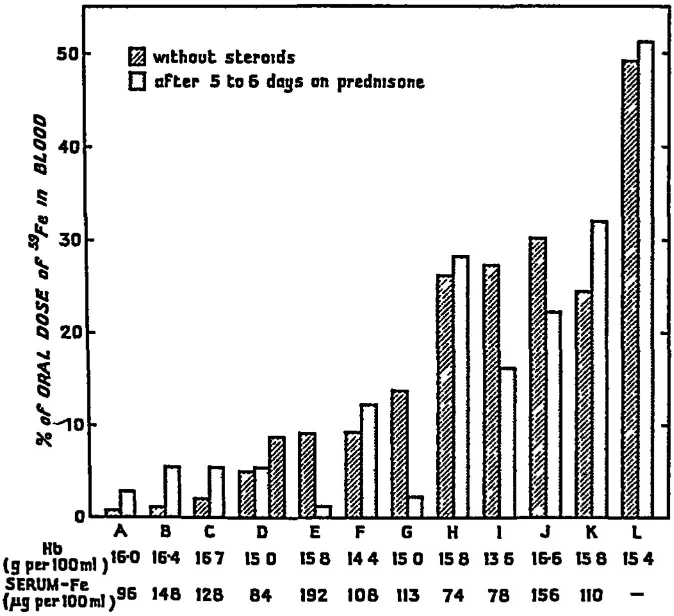


Fig 1—Effect of administration of steroids on absorption from 5 mg ^{59}Fe in control subjects

days before and 1–2 days after the dose of iron was given, or as corticotrophin 40 units intramuscularly daily for 3–4 days prior to the test.

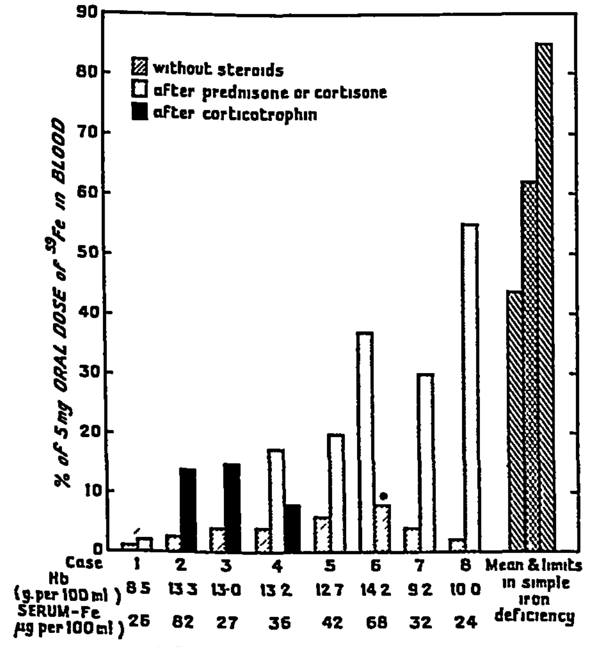
The effect of the gluten-free diet was assessed after it had been taken for periods ranging from 6 weeks to 1 year.

Results

Effect of Steroids

In the twelve control subjects (fig 1) treated with prednisone 40 mg daily for 5–6 days there was no constant alteration in the amount of labelled iron which appeared in the red cells.

In uncomplicated iron deficiency some 45–83% (mean 61%) of a 5 mg oral dose of iron will appear in the red cells (Smith and Mallett 1957). In contrast, all the patients with steatorrhœa, including those with severe iron deficiency, showed greatly diminished absorption (less than 8%, mean 3·6%) (fig 2). Following treatment with prednisone or cortisone, the absorption of iron was increased to between 17·5 and 55% in every patient but one, with a mean of 27%. The exception (case 1) was a very severe longstanding case in which, even after 3 weeks' treatment with prednisone, less than 2% of the dose of oral iron was absorbed. Although the improvement in absorption following steroids was considerable in the others, in only three patients did it rise to levels comparable to those in simple iron deficiency.



* Off steroids 1 week before test

Fig 2—Effect of administration of steroids on absorption from 5 mg ^{59}Fe in patients with steatorrhœa

In case 6 the 37% absorption of iron was obtained after a year's treatment with cortisone for an accompanying rheumatoid arthritis. The cortisone was discontinued and the test repeated after only 1 week without steroids. The absorption had already dropped to 8%, although the patient's general condition remained excellent and she had no diarrhœa.

Corticotrophin was administered to three patients and improvement in absorption was noted in all, but the difference was not as clear as that following the oral steroids.

Effect of Gluten-free Diet

Following treatment with gluten-free diet, all the subjects noted improvement in their symptoms with a decrease in the diarrhœa, but the absorption of iron was not always increased, and only in case 3 was the improvement as dramatic as that following the steroids (fig 3). Case 3 was a young man with undoubted cœliac disease with hospital records going back to childhood, the improvement in absorption from 4 to 37% occurred after he had been only 6 weeks on the diet. The three others (cases 7–9) who showed fair improvement had had symptoms in childhood with presumptive evidence of cœliac disease. Cases 2, 4, and 10 had short histories with onset in adult life.

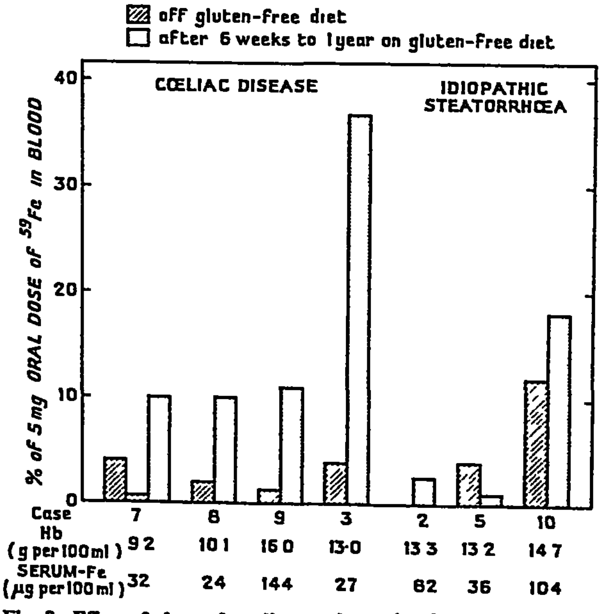


Fig 3—Effect of gluten-free diet on absorption from 5 mg ^{59}Fe in patients with steatorrhœa

Discussion

These studies provide evidence that both corticosteroids and a gluten-free diet may improve absorption of iron in patients with idiopathic steatorrhœa and cœliac disease.

The way in which the improvement is brought about remains obscure. Normally, in response to iron deficiency, an increased amount of iron is absorbed through the intestinal cell. In the iron deficiency associated with idiopathic steatorrhœa and cœliac disease this does not occur. In these conditions the defect in iron metabolism appears to be solely in absorption, as parenterally administered iron is utilised normally. This suggests that the improvement following steroids is due to a direct effect on the intestinal cell which can be brought about both by oral and parenteral treatment. It is unlikely to be due to a non-specific change in the permeability of the intestinal cell. If it were, a similar effect should be evident in the control subjects, and we have been unable to demonstrate this.

Cœliac disease is now believed to be due to a sensitivity to wheat gluten, although the exact mechanism is not understood. It might be postulated, therefore, that the steroids exert a beneficial effect on iron absorption in cœliac disease and adult steatorrhœa by suppressing an abnormal antigen-antibody reaction.

Summary

Studies with radioactive iron have shown that there is gross malabsorption of iron in patients with idiopathic steatorrhœa and cœliac disease.

The absorption may be rapidly improved by the administration of cortisone, prednisone or corticotrophin, but decreases equally rapidly as soon as the drugs are stopped. In control subjects steroids have no such constant effect.

In cœliac disease a gluten-free diet improves the absorption of iron.

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RECENT CHANGE IN BLOOD-GROUP DISTRIBUTION OF ASTROCYTOMAS

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In an investigation into the ABO blood-group distribution in cerebral tumours Mayr et al. (1956) found, in 385 gliomas of all types, no significant difference from the general population. On the other hand, in a report on the first five years of the Manchester Children's Tumour Registry (1954–58) Steward (1959) noted an unusual preponderance of group A among children with gliomas. In both these series the numbers for individual glioma types were small. We report here our findings in 473 astrocytomas which indicate an apparent change in recent years in the blood-group patterns in this disease.

The diagnosis was based on a recent reassessment of the pathological material by one of us (P. O. Y.), tumours showing glioblastomatous features were excluded. The ABO blood-grouping was taken from the case-records and was that performed at the time of admission to hospital for surgical treatment. The cases were derived from neurosurgical centres in Manchester, which drain an area similar to that covered by the Manchester regional transfusion service. For this reason the ABO figures from the latter have been used as controls (Stratton 1953). Because these figures, relating to blood-donors, are those for the adult population, and we wished to exclude any significant population changes in recent years, we collected a control series of blood-groups in children. This consisted of 843 children under 15 years admitted to Manchester hospitals during the years 1947–58 for the treatment of burns. Table I shows that the ABO distribution in this series is very close to that of the general adult donor population. We have therefore used the latter throughout for statistical comparison. For this purpose the figures of groups B and AB, being usually small, have been combined.

TABLE II—DISTRIBUTION OF BLOOD-GROUPS IN ASTROCYTOMAS ACCORDING TO YEAR OF DIAGNOSIS

Year	A	B	AB	O	Total
1933–35	4			9	13
1936–40	26	4	1	28	59
1941–45	36	4	2	50	92
1946–50	42	11	5	34	92
1951–55	60	17	8	56	141
1956–58	43	5	3	25	76
Before 1946	66 (*40.2%*)	8 (*4.9%*)	3 (*1.8%*)	87 (*53%*)	164
After 1945	145 (*46.9%*)	33 (*10.7%*)	16 (*5.3%*)	115 (*37.2%*)	309

A superficial examination of the figures for astrocytomas as a whole (table I) does not reveal any great change from the controls ($\chi^2_{[2]} = 6$, $P = 0.05$) but there is some reduction in the percentage of group O and a corresponding increase of A. The difference, though small, is unlikely to be fortuitous. There does not appear to be the degree of preponderance of A suggested by the figures from the Manchester Children's Tumour Registry for the past five years.

When, however, the cases are arranged according to the year in which diagnosis and blood-grouping was carried out (table II) a change of pattern appears after 1945. Those before that date show the expected distribution, those after show a very significant reduction of group O ($\chi^2 = 17$, $P = 0.0002$). It might be argued that, if children with astrocytomas have always shown a reversal of the blood-group A/O ratio, then greater numbers of children in the second period would produce an apparent change in the pattern of astrocytomas as a whole. In the cases under 20 years of age (table III) there is a highly significant change of pattern with an increase of A, B, and AB at the

TABLE I—INCIDENCE OF ASTROCYTOMAS ACCORDING TO BLOOD-GROUPS

—	A	B	AB	O	Total
Controls					
Adult population of N.W. region	3775 (*40.3%*)	788 (*8.4%*)	275 (*2.9%*)	4532 (*48.4%*)	9370
Children admitted to hospital with burns (1947–58)	329 (*39%*)	66 (*7.8%*)	31 (*3.7%*)	417 (*49.5%*)	843
Astrocytomas	211 (*44.5%*)	41 (*8.7%*)	19 (*4.0%*)	202 (*42.7%*)	473

TABLE III—DISTRIBUTION OF BLOOD-GROUPS IN ASTROCYTOMAS UNDER AGE OF 20 ACCORDING TO YEAR OF DIAGNOSIS

Year	A	B	AB	O	Total
Before 1946	13 (*25·5%*)	3 (*6·1%*)	2 (*4·1%*)	31 (*63·3%*)	49
After 1945	53 (*54·1%*)	12 (*12·2%*)	9 (*9·2%*)	24 (*24·5%*)	98

expense of O. For the period after 1945 $\chi^2_{[2]}=25·2$; $P<0·00001$. At this point it is necessary to provide some indication that faults in blood-grouping technique in earlier years are not a contributory factor. For this purpose we give the figures for 322 meningiomas (table IV) which have shown a fairly constant normal blood-group distribution throughout the years.

The change observed in the under-20 age-group suggests that the phenomenon may be more closely linked with year of birth rather than year of diagnosis. Analysis according to year of birth (table V) shows that, whilst those born before 1931 have a fairly normal distribution of blood-groups, those born after 1930 show a considerable proportional reduction of group O ($\chi^2_{[2]}=20·8$; $P<0·00003$).

TABLE IV—BLOOD-GROUP DISTRIBUTION OF MENINGIOMAS ACCORDING TO YEAR OF DIAGNOSIS

Year	A	B	AB	O	Total
1931–35	4	0	0	7	11
1936–40	14 (*35%*)	6	2	17 (*43%*)	39
1941–45	19 (*41·3%*)	5	0	22 (*48%*)	46
1946–50	26 (*41·3%*)	6	2	29 (*46%*)	63
1951–55	44 (*44%*)	4	5	46 (*46%*)	99
1956–58	24 (*37·5%*)	6	0	34 (*53%*)	64
Before 1946	37 (*38·6%*)	11 (*11·5%*)	2 (*2·1%*)	46 (*48%*)	96
After 1945	94 (*41·6%*)	16 (*7·1%*)	7 (*3·1%*)	109 (*48·2%*)	226
Total	131 (*40·7%*)	27 (*8·4%*)	9 (*2·8%*)	155 (*48·1%*)	322

Discussion

The proportion of cases which have been examined for ABO blood-groups has varied from time to time according to factors such as surgical technique, fashions in surgical treatment, and changes of clinical staff. It seems unlikely that any alteration of the distribution of groups within a tumour type could result from such factors. A more likely source of error would be increasing skill and experience of laboratories in blood-grouping techniques, but a changing pattern from this cause should not discriminate between tumour types. The lack of change in the meningiomas suggests that faults in blood-grouping were never great enough to be statistically appreciable.

TABLE V—DISTRIBUTION OF BLOOD-GROUPS IN ASTROCYTOMAS ACCORDING TO YEAR OF BIRTH

Year	A	B	AB	O	Total
1871–90	7	2	0	11	20
1891–1900	25	4	3	41	73
1901–10	45	8	2	42	97
1911–20	32	7	3	28	70
1921–30	37	6	2	45	90
1931–40	28	6	4	18	56
1941–50	30	7	4	15	56
1951–55	7	1	1	2	11
Before 1931	146 (*41·7%*)	27 (*7·8%*)	10 (*2·9%*)	167 (*47·7%*)	350
After 1930	65 (*52·8%*)	14 (*11·4%*)	9 (*7·3%*)	35 (*28·4%*)	123

We cannot completely exclude the possibility of a change in blood-group pattern in this region due to migration, since we have been unable to obtain an adequate control series of children grouped before 1945, but the close agreement between our children with burns and the adult blood-donors (who were presumably children in the earlier period) would suggest that this is not significant. This is supported by the stability, through the years, of the ABO distribution of the meningiomas.

An increasing programme of immunisation in childhood, using antigens many of which may contain blood-group substances, will alter the antibody status of the serum of a considerable proportion of the population. But this is unlikely to have affected the red blood-cells, and our control series of children with burns shows in fact a normal blood-group pattern.

The astrocytomas are not a homogeneous group. They show various degrees of growth activity and of differentiation; they can also be divided into an adult type, almost confined to the cerebral hemispheres, and a juvenile type. The latter is known by many names, including cerebellar astrocytoma, optic-nerve glioma, piloid glioma, and spongioblastoma. The change in blood-group distribution occurs in both types, but since it is a feature of youth it is much more obvious in the juvenile astrocytoma. It would not be useful to present here figures for the various anatomical sites and pathological subtypes. Our impression is that the phenomenon we have described is present in all.

Until our results are confirmed or refuted from other centres it is not profitable to speculate about the underlying causes. We cannot yet be certain whether there is a rise in the incidence of astrocytomas in people of groups A, B, and AB or a fall in those of group O. Possibly some factor has appeared facilitating regression of astrocytomas in people of group O similar to the known regression in the clinically more obvious retinoblastomas.

In recent years many reports have pointed to an abnormal distribution of blood-groups in disease. We are not aware of any in which a change in the pattern has been reported. It seems, however, that if our observation that the change first appears in those born after 1930 is confirmed, then it will still be apparent only in diseases which are common in children and young adults.

Summary

An investigation of the ABO blood-group distribution in 473 astrocytomas shows a slight reduction in the proportion of group O when the cases are considered as a whole ($\chi^2_{[2]}=6$, $P=0·05$).

The figures have been analysed according to the year of diagnosis. Whereas before 1946 the blood-groups were distributed normally, after 1945 there is a very significant reduction of group O ($\chi^2_{[2]}=17$, $P=0·0002$). This is shown to be largely due to a change in the blood-group distribution in children and young adults with astrocytomas. This phenomenon is present in those born after 1930 ($\chi^2_{[2]}=20$, $P<0·00003$), those born before that date showing a normal pattern.

We thank Mr B. D. Dawson, Mr A. N. Guthkelch, Mr R. T. Johnson, and Mr J. M. Potter, who allowed us to examine the case-notes of their patients, Dr H. B. Marsden for some of the pathological material, Miss R. Davidson and Mr J. C. Hughes for help in searching records, and the records officers of the hospitals concerned for their cooperation.

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EFFECT ON SERUM-CHOLESTEROL LEVEL OF REPLACEMENT OF DIETARY MILK FAT BY SOYBEAN OIL

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DURING recent years the possible relationships between dietary fats and blood-lipids, particularly cholesterol, on the one hand and between blood-lipids and atherosclerosis on the other have aroused much interest These problems are of great practical significance in Finland, where the consumption of fats is high (Roine et al 1958), serum-cholesterol values unusually high, and the atherosclerotic diseases very common (Keys et al 1958) It has been demonstrated beyond doubt that changes in dietary fats will alter the serum-cholesterol values, although there does not yet seem to be complete unanimity about the effects of different fatty acids and other components of natural fats and oils in this respect (Ahrens et al 1957, Beveridge et al 1958, Horlick and Craig 1957, Keys et al 1957, Kinsell and Sinclair 1957) There is also considerable evidence in favour of the view that high blood-lipid values may be conducive to atherosclerosis, although this question can hardly be regarded as settled

TABLE I—COMPOSITION OF DIETS IN THE HOSPITALS BEFORE AND AFTER THE DIETARY CHANGE (CONSUMPTION PER CAPUT PER DAY)

—	Hospital E		Hospital C	
	Before change (Aug '58)	After change (Feb '59)	Before change (Aug '58)	After change (Feb '59)
Energy (k cal)	3018	2974	3058	2925
Proteins (g)	107	103	104	100
Fats				
Amount (g)	114	106 5	120	115
% of total food energy	34 0	32 2	35 3	35 4
Fatty acids (g)				
Saturated	59·4	42 6	60 6	60 3
Monoethenoids	40 0	38 1	42 5	39 0
Linoleic acid	7 6	16 8	8 8	8·0
Other polyenthenoids	1 5	4·4	2 2	2 1

There were no appreciable differences in carbohydrate, mineral, or vitamin content of the diets between the two hospitals

The studies of which this is a preliminary account were started in the autumn of 1958 with the aim of ascertaining (1) whether it was possible to devise dietary changes which would be acceptable in the long run, and at the same time would cause a substantial decrease in serum-cholesterol values, and (2) whether such a lowering of serum-cholesterol would have any effect on the development of atherosclerotic manifestations While the first part of this work could obviously be carried out in a relatively short time, it was evident that the second part would require a rather long period of observation—at least a few years

Method

For this work two mental hospitals in the vicinity of Helsinki were selected In one of these (hospital E) the dietary changes described below were instituted, while the other (hospital C) was kept as the control hospital Hospital E had 1100 beds, and hospital C had 640 beds

Diets

The food consumption before the experiment was similar in the two hospitals To the total food energy various constituents contributed as follows

	Hospital E	*Hospital C*
Cereals (*mainly wheat and rye*)	29%	24%
Meat	10%	10%
Potatoes	10%	10%
Sugar	7%	12%
Milk	20%	18%
Butter	9%	9%
Margarine	4%	5%

Total daily consumption of fats was in hospital E 114 g and in hospital C 120 g This quantity comprised

	Hospital E	*Hospital C*
Milk fat	57%	52%
Meat fat	19%	19%
Margarine fat	12%	14%
Vegetable oils	2%	4%

The diet in hospital E was changed in two respects First, whole milk was replaced by a 3 5% emulsion of soybean oil in skim milk The oil used was fortified with vitamins A and D so that the final product contained 70 I U of vitamin A and 10 I U of vitamin D per 100 ml Secondly, butter and margarine were replaced by a special brand of margarine considerably more unsaturated than any of the brands marketed in Finland Its iodine value was 78–80, and its content of chief unsaturated fatty acids was as follows oleic 28%, linoleic 15 8%, and linolenic 4 9% The main effect of these dietary changes was that the milk fat present in the original diet was almost totally replaced by vegetable oils, mainly soybean oil

TABLE II—FOOD ENERGY DERIVED FROM TWO GROUPS OF FATTY ACIDS (% OF TOTAL ENERGY) BEFORE AND AFTER THE DIETARY CHANGE

—	Hospital E		Hospital C	
	Before change (Aug '58)	After change (Feb '59)	Before change (Aug '58)	After change (Feb '59)
Saturated fatty acids	17 7	12 9	17 9	18·6
Linoleic and other polyethenoid acids	2 7	6 4	3 2	3 1
Ratio saturated/polyethenoids	6 6/1	2 0/1	5·6/1	6·0/1

The composition of the diets in hospital E and hospital C before and after the dietary change is shown in table I This table shows that the fatty-acid composition remained very nearly the same in hospital C In hospital E, however, the dietary change resulted in a very definite change in the fatty-acid composition of the diet The amount of saturated acids consumed decreased considerably, while consumption of linoleic and other polyethenoid acids increased Table II shows the percentages of food energy derived from these two groups of fatty acids before and after the dietary change in both hospitals

Serum-cholesterol Values

To follow the effects of dietary changes on blood-lipids a group of male patients 35–64 years of age was randomly selected in each hospital The total serum-cholesterol of each subject was determined before and after the dietary change A modification (Anderson and Keys 1956) of the method of Abell et al (1952) was used

Results

The results are shown in table III In hospital E, in which the diet was changed as described above, the mean

TABLE III—SERUM-CHOLESTEROL VALUES BEFORE AND AFTER THE DIETARY CHANGE

—	Hospital E	Hospital C
No of patients	117	53
Mean age (yr)	49 8	48 3
Mean serum cholesterol (mg per 100 ml)		
Before dietary change (Aug '58)	235 7	252 7
After dietary change (Feb '59)	215 3	26[illegible] 7
Cholesterol change (mg per 100 ml)	−20 4	9 6
s E	±3 2	±5 7
t	6 4	1 7
P	<0·001	0 1

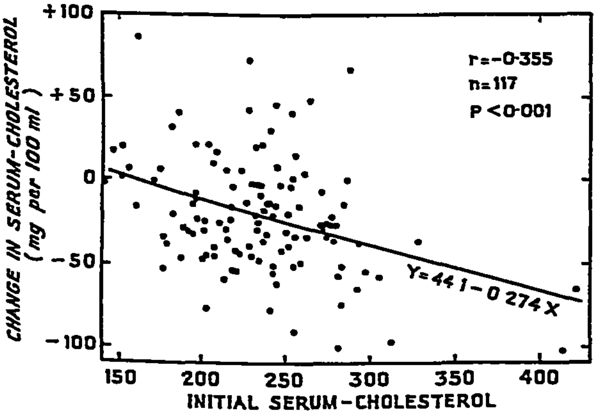
TABLE IV—PREDICTED * AND OBSERVED MEAN SERUM-CHOLESTEROL VALUES (MG PER 100 ML.) AFTER THE DIETARY CHANGE

—	No of patients	Before change (G)	After change		
			Predicted * (G)	Observed	Difference
Hospital E					
All	117	235·7	215·8	215·3	+0·5
"Highs"	59	268·7	243·7	241·4	−2·3
"Lows"	58	202·1	187·3	188·7	−1·4
Hospital C	53	252·7	255·2	262·3	−7·1

* According to Keys et al (1959)

blood-cholesterol decreased appreciably—i.e., from 236 mg to 215 mg per 100 ml. serum. In hospital C, in which the normal house diet was continued, there was, on the contrary, a slight increase in blood-cholesterol—i.e., from 252 mg to 262 mg. To assess the statistical significance of this change the difference in serum-cholesterol between the value before and that during the experiment was computed individually for each patient, and further the mean and standard error of this mean were calculated. The decrease in mean serum-cholesterol value observed in hospital E proved to be statistically highly significant, while the increase in hospital C was not significant by customary standards.

There were large individual variations in the serum-cholesterol response to the dietary change, which was obviously influenced by several factors. One of these is the height of the serum-cholesterol value before the dietary change (Keys et al. 1959). The higher the initial serum-cholesterol the greater its decrease tends to be. This is shown in the accompanying figure—a correlation diagram in which the change of serum-cholesterol is plotted against the initial serum-cholesterol value. There is a definite negative correlation between these two factors. The correlation coefficient is



Correlation between the change in the serum-cholesterol value and the initial level.

$$r = -0.355$$

a value which, though not particularly high, is nevertheless highly significant ($n=117$, $P<0.001$). The dependence of the serum-cholesterol change (Y) on the initial serum-cholesterol value (X) is defined by the regression equation

$$Y = 44.1 - 0.274\,X$$

Keys et al. (1959) have developed equations purporting to predict the changes in serum-cholesterol values which follow changes in fatty-acid composition of the diet. We have applied such a prediction equation to our data. Since our groups of patients differ from the reference group of Keys et al. both in initial serum-cholesterol value and in the composition of their diet, we had to use the more general type of equation

$$G_3 = 0.91\,(Z_2 - G_2 - Z_3) + 1.91\,G_2 Z_3 / Z_2$$

In this equation G_2 and G_3 refer to mean serum-cholesterol values before and after the dietary change, respectively. Z_2 and Z_3 are factors which are computed from the fatty-acid composition of diets as follows

$$Z_2 = 175 + 2.68\,S_2 - 1.23\,P_2 \text{ and}$$
$$Z_3 = 175 + 2.68\,S_3 - 1.23\,P_3,$$

where S_2 and S_3 refer to percentages of the total food energy contributed by glycerides of saturated fatty acids before and after the dietary change, respectively, and P_2 and P_3 refer to the corresponding percentages contributed by glycerides of polyethenoid fatty acids.

The predicted and the observed serum-cholesterol values after dietary change appear in table IV. In hospital E the prediction was carried out not only for the whole group as such but also for the group divided into two subgroups the "highs", having initial serum-cholesterol values above the mean of the whole group, and the "lows", having serum-cholesterol values below the mean. There is excellent agreement between the prediction and the observation in the material from hospital E. In hospital C, though there was no intentional change, the fatty-acid composition of the diet did not remain quite the same. The prediction equation also indicated a change —namely, a slight increase—while the observed change was a somewhat greater increase. In view of the relatively large variation of serum-cholesterol, in this case, too, the agreement between the prediction and the observation is good.

Discussion

The dietaries in these hospitals are typical of Finnish dietaries in general in that they contain large quantities of whole milk and butter. The work reported here shows that the replacement of whole milk by a soybean-oil emulsion in skim milk, and that of butter by a special type of margarine, results in a statistically highly significant, though not very large, decrease in the mean serum-cholesterol value. The practical significance of this change is somewhat increased by the fact that the subjects with higher initial serum-cholesterol levels also tend to show greater decreases. It is not yet clear whether this relatively modest lowering of serum-cholesterol will have any effect on the frequency of coronary-artery disease and other atherosclerotic manifestations, but we hope that the clinical and electrocardiographic investigations now in progress will soon shed light on this point. Quite possibly we shall have to devise means to reduce serum-cholesterol further in order to influence the development of these pathological processes. This could perhaps be accomplished by, for example, further increasing the degree of unsaturation of the component fats of the margarine.

Summary

The ordinary house diet of a mental hospital was changed by replacing whole milk by an emulsion of soybean oil in skim milk and by replacing butter and margarine by a special brand of margarine considerably more unsaturated than the ordinary margarines marketed in Finland.

These changes decreased the saturated-fatty-acid content of the diet and increased its content of linoleic and other polyethenoid acids.

After this dietary change the mean serum-cholesterol

value of the 35–64-year-old male patients decreased from 236 mg to 215 mg per 100 ml serum This decrease was statistically highly significant

We wish to express our gratitude to Mr Heikki Kerkkonen, Parma Ltd , and to Dr Matti Antila, of Raisio Factories, for the development of the special milk and margarine products used in this work

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EARLY SYMPTOMS OF PRE-ECLAMPTIC TOXÆMIA

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IN previous work on pre-eclamptic toxæmia certain warning symptoms were noted well in advance of any signs (Dalton 1954) This finding has since been corroborated in the course of trials of the prophylactic value of progesterone Patients between the 16th and 28th weeks of pregnancy were asked " Do you feel as well now as before you became pregnant ? ", and the subsequent history of the pregnancy has been found to differ in those who said " yes " and those who said " no "

At the antenatal clinic of the Obstetric Hospital, University College Hospital, London, between the years 1955 and 1958 the registrars put this question to 386 patients attending for routine examination at the 16th or 28th week (first series), and in 1958 I questioned 247 patients attending for examination at any time between the 16th and 28th weeks of pregnancy (second series) Patients who said that they felt less well than before their pregnancy were asked if this was due to nausea and vomiting, headaches, backaches, vertigo, fainting, paræsthesia, or lethargy In the second series those with symptoms were also asked if they felt depressed, and in addition a note was made of those patients who felt better than usual

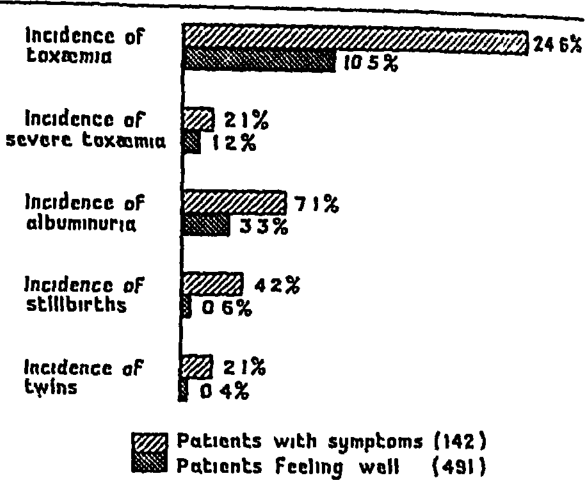
In this investigation pre-eclamptic toxæmia was diagnosed if a woman, previously free from hypertension and albuminuria, was found after the 28th week to have a blood-pressure of 140/90 mm Hg or over, with œdema or with albumin in a catheter specimen

Results

Of the 670 patients who were questioned 12 were excluded because antenatal care was not completed (abortion or cancelled booking) and 25 had a blood-pressure of at least 140/90 before the 28th week Of the remaining 633, 491 (78%) said that they felt well and 142 (22%) had symptoms The striking difference in the incidence of toxæmia in these two groups is shown in table I of the women who had symptoms between the 16th and 28th week, one in every four developed toxæmia, compared with one in every ten who had felt well

TABLE I—INCIDENCE OF TOXÆMIA

Patients	Series	Toxæmia	Normal	Total
With symptoms	1st 2nd	13 (25%) 22 (21%)	39 69	51 91
	Total	35 (25%)	107	142
Feeling well	1st 2nd	31 (10%) 18 (12%)	301 139	335 156
	Total	52 (11%)	439	491



Differences between patients with symptoms and those feeling well between the 16th and 28th weeks of pregnancy

The figure shows that the patients with symptoms during the middle trimester also had double the incidence of a more severe grade of toxæmia (with a blood-pressure of at least 140/90 mm Hg, and both œdema and albuminuria), double the incidence of albuminuria, a higher stillbirth-rate, and more twin pregnancies The incidence of œdema was not significantly different (33% in patients with symptoms compared with 37% in patients feeling well)

TABLE II—SYMPTOMS IN THE MIDDLE TRIMESTER

—		Toxæmia	Normal
Nausea and vomiting	(142 patients)	65%	71%
Headache	(,, ,,)	35%	42%
Backache	(,, ,,)	11%	51%
Lethargy	(,, ,,)	88%	78%
Vertigo	(,, ,,)	26%	20%
Fainting	(,, ,,)	12%	9%
Paræsthesia	(,, ,,)	46%	30%
Depression	(91 patients)	52%	50%

In the second series 33 patients (13%) said they had felt better than usual since becoming pregnant Of these 3 (9%) developed toxæmia, and 1 (3%) developed albuminuria, there were no stillbirths or twins and 13 patients (39%) developed œdema Thus there was little difference between the patients who felt well and those whose wellbeing had actually improved with pregnancy

142 women complained of symptoms, and little difference is apparent in the symptoms of those who afterwards developed toxæmia and those who did not (table II)

An analysis of the number of symptoms suggests that these women did not lightly complain, for 91% had at least two unrelated symptoms, 71% had three, and 49% had at least four At another London maternity hospital, I found that 72% of 136 patients had three or more unrelated symptoms and 51% admitted to *four or more* (Dalton 1957)

In the second series some patients were interviewed more than once Of 74 patients with symptoms on only one occasion, 20% developed toxæmia, whereas among the 17 whose symptoms persisted from one interview until the next (a month later) 41% did so. The series was also analysed as regards the duration of pregnancy at the time of the interview, but no difference was found in the incidence of toxæmia among patients with symptoms and among those feeling well at the 4th, 5th, or 6th month of pregnancy.

Discussion

The presence of symptoms between the 16th and 28th weeks of pregnancy suggests that the factor responsible for pre-eclamptic toxæmia is already operating many weeks before the development of signs. Further it suggests that in any patient who has symptoms—even if there are no signs and no excessive gain in weight—prophylactic treatment of toxæmia should begin during the middle trimester. The similarity in type and distribution of symptoms among those patients afterwards developing toxæmia and in those whose pregnancies proceed normally suggests that the patients with continuing symptoms may have subclinical toxæmia.

Summary

In a series of 633 patients one in every four women with symptoms between the 16th and 28th weeks of pregnancy subsequently developed toxæmia, compared with one in every ten women who were feeling well during these middle months. Those with symptoms during the middle trimester also had a greater incidence of albuminuria, stillbirths, and twins. It is suggested that patients with symptoms during pregnancy should be treated with a toxæmic prophylactic regime even in the absence of signs or excessive weight gain.

It is a pleasure to express my thanks to Prof W C W Nixon for allowing me to carry out these trials in his hospital and to his registrars for their assistance, and to Prof D D Reid for his statistical assistance.

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ANTITUBERCULOUS THERAPY COMBINED WITH ADRENAL STEROIDS IN THE TREATMENT OF PLEURAL EFFUSIONS

A CONTROLLED THERAPEUTIC TRIAL

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Several authors have reported favourably on the use of adrenal steroids combined with antituberculous drugs in the treatment of tuberculous pleural effusions (Sors and Trocme 1954, James 1956, Aspin and O'Hara 1958), but as far as we are aware no controlled therapeutic trial has so far been carried out. Such a trial was designed to evaluate this method of treatment in African mine labourers employed in the goldmining industry of the Witwatersrand, among whom pleural effusions are relatively common.

In selecting cases for the trial we were faced with the difficulty that some medical officers concerned with the care of African mine labourers doubt whether tuberculosis is the major cause of pleurisy with effusion in this population. This view is based on the fact that it is unusual to isolate tubercle bacilli from the pleural fluid. Because of the extremely high incidence of pneumonia among these patients, some doctors are of the opinion that a substantial number of cases are postpneumonic in origin. Others consider that scurvy, which is not rare, may account for those effusions which are hæmorrhagic (approximately a third of the total). Nevertheless, we regard the majority of cases, including the hæmorrhagic ones, as tuberculous. This is supported by the high incidence of tuberculosis in these labourers, by the thoracoscopic findings (Fleishman et al 1956), and by the follow-up study of Stott and Brass (1955). The diagnosis of tuberculous pleural effusion in the cases entering the trial was based, therefore, on evidence which, though presumptive, is generally regarded as sound. This evidence has been reviewed by Roper and Waring (1955).

It is for these reasons that the trial included four different methods of treatment—namely, ascorbic acid, penicillin, standard antituberculous therapy, and standard antituberculous therapy combined with adrenal steroids. It was hoped that the inclusion of groups receiving ascorbic acid and penicillin, while acting as bases from which to judge any improvement effected by the other two methods of treatment, would shed some light on the role of scurvy and of pneumonia in the pathogenesis of the cases studied.

Design of the Trial

From June 1, 1957, to September 26, 1958, all cases of pleural effusion which occurred among the African labourers employed by one group of mining companies were admitted to a central hospital as soon as the diagnosis was confirmed by X-ray examination of the chest and by aspirating 20 ml of fluid from the pleural cavity. Referring medical officers were requested to limit the paracentesis to 20 ml so that the possible beneficial effects of removing larger amounts were avoided. Although the disadvantages of examining so small a quantity of fluid were realised, it was nevertheless submitted to full examination including a culture and a biological test for tubercle bacilli.

On admission to the central hospital a full clinical examination was carried out and another X-ray film of the chest taken for confirmation. Patients showing evidence of pulmonary tuberculosis or of any pathology other than the effusion were rejected. In addition, a few cases with cervical or other adenopathy, abdominal masses, and vitamin deficiency were excluded. Consequently those admitted to the trial could be described as suffering from pleural effusion for which no obvious clinical or radiological cause was evident. A blood count, erythrocyte-sedimentation rate (E.S.R.) (Wintrobe), Mantoux skin test (Koch's old tuberculin 1/1000), and sputum examinations completed the initial investigations.

A panel of 5 doctors allotted a score to the effusion ranging from 1 to 4, depending upon whether it was judged to occupy $^1/_4$, $^1/_2$, $^3/_4$, or the whole of the hemithorax respectively. Occasionally it was found necessary to allot $^1/_2$ scores—e.g., $2^1/_2$. Minimal effusions were not accepted. Sealed instructions for treatment were previously prepared, and as each case was admitted to the trial a member of the hospital clerical staff drew one, so that the following four methods of treatment were allocated at random.

Treatment I. 500 mg of ascorbic acid intramuscularly daily for the first 14 days only.

Treatment P. 300,000 units of procaine penicillin intramuscularly twice daily for the first 14 days only.

Treatment T. 1 g of streptomycin sulphate intramuscularly daily for 8 weeks. 200 mg of isoniazid three times daily for 8 weeks.

TABLE I—ANALYSIS OF AVERAGE WEIGHTS AND SEDIMENTATION-RATES

Treatment group	Average weight (lb)		Average E.S.R (mm /hr) (Wintrobe)	
	Initial	Final	Initial	Final
V	127	130	22	14
P	131	131	25	18
T	130	134	29	20
TS	132	138	22	4

Treatment TS Same as treatment T, with the addition of 10 mg of prednisolone (' Deltacortef ') three times daily for 2 days followed by 5 mg three times daily for the remainder of the 8 weeks

All patients received a standard hospital diet and in addition, 3 tablets of vitamin B Co * daily The period of bed rest varied from case to case depending on the general condition of each patient, but when allowed up, all patients were confined to the precincts of the ward The X-ray examination of the chest and E S R were repeated at the end of 4 weeks, at which time the panel reviewed each patient without knowledge of the type of treatment given This process was repeated at the completion of the trial at the end of 8 weeks

2 patients receiving treatment V and 2 receiving treatment P were withdrawn from the trial and given treatments T or TS because it was felt that they were so ill that the withholding of antituberculous therapy was not justified

Results

75 patients completed the trial, 19 of them having received ascorbic acid (treatment V), 17 penicillin (treatment P), 19 antituberculous drugs (treatment T), and 20 antituberculous drugs combined with steroids (treatment TS)

The pleural fluid was noted to be hæmorrhagic to a greater or lesser degree in 8 cases in group V, 5 in group P, 6 in group T, and 9 in group TS

One patient in group V and another in group P had bilateral effusions, and these were omitted from the statistical analysis, leaving a total of 73 cases for assessment

The sputum examination was negative for tubercle bacilli in all cases entering the trial

The tuberculin skin test was positive in all but 1 case This patient received treatment TS

In only 1 instance were tubercle bacilli found in the pleural fluid and that to direct examination only He received treatment P Due to an oversight, this result became known only at the completion of his course of treatment

The initial and final average weights and sedimentation-rates appear in table I and suggest an advantage in favour of group TS

In table II are set out the individual details with regard to the extent of the effusion initially, after 4 weeks and after 8 weeks of treatment It will be seen that the cases were fairly evenly distributed and that the average initial size of the effusions was similar in each treatment group Standard statistical techniques indicate that neither after 4 weeks nor at the completion of the trial was there a significant difference in the rate of clearing of fluid between groups V, P, and T

TABLE III—AVERAGE OVERALL IMPROVEMENT

Treatment	V	P	T	TS	
C_1-C_2	0·639	0 531	0 658	1 885	First 4 weeks
Estimated standard deviation	0 228	0 161	0 184	0 259	
C_2-C_3	0 500	0 219	0 237	0 325	Second 4 weeks
Estimated standard deviation	0 153	0 111	0 072	0·097	
C_1-C_3	1 139	0 750	0 895	2 210	All 8 weeks
Estimated standard deviation	0 189	0 165	0 182	0 218	
Maximum possible average improvement = C_1	2·583	2 688	2 316	2 735	

On the other hand, a highly significant improvement took place in group TS compared with groups V, P, and T within the first 4 weeks, although no further significant improvement occurred in this group during the subsequent 4 weeks of treatment The various differences and their associated standard deviations are given in table III

TABLE II—CHANGES IN EXTENT OF EFFUSION

Treatment	V				P				T				TS			
	P	C_1	C_2	C_3	P	C_1	C_2	C_3	P	C_1	C_2	C_3	P	C_1	C_2	C_3
	52	1	0	0	49	1	0	0	18	1	0	0	32	1	0	0
	50	1½	1	1	66	1	1	½	39	1	½	0	22	1½	0	0
	1	2	1	1	48	1½	2	½	59	1	2½	2	58	1½	½	0
	20	2	4	1½	45	2	1½	2	21	1½	1½	1	3	2	2	1
	25	2	1½	1	65	2	2	2	71	1½	0	0	6	2	1	1
	26	2	2	1½	80	2	0	0	9	2	1	1½	17	2	0	0
	24	2½	1	1	5	3	2	2	12	2	0	0	55	2	½	½
	31	2½	2½	2	14	3	2	1½	28	2	½	½	68	2	2	1
	44	2½	1	0	15	3	2½	2	41	2	1½	1	30	2½	1	0
	61	2½	2	1	23	3	3	2½	53	2	2	2	60	2½	0	0
	70	2½	2	1½	33	3	2½	2½	47	2½	1	1	74	2½	0	0
	11	3	3	3	56	3	2½	2½	10	3	3	2½	13	3	0	0
	16	3	3	2	57	3½	3	3	34	3	1½	½	43	3	0	0
	46	3	½	½	8	4	4	4	51	3	2½	2½	67	3	½	0
	40	3½	3	3	27	4	2½	2	69	3	2½	2½	7	4	3	2
	64	3½	1½	½	54	4	4	4	72	3	2	2	36	4	0	0
	75	3½	3	2½					81	3	3	3	37	4	0	0
	4	4	3	3					78	3½	3	2½	38	4	3	3
									19	4	3½	3½	63	4	2½	1
													79	4	1	1
No of cases	18				16				19				20			
Average condition		C_1 2 583	C 1·944	C_3 1·444		C_1 2 688	C_2 2 157	C_3 1·938		C_1 2 316	C_2 1·658	C_3 1·421		C_1 2 735	C_2 0 850	C_3 0 525
Average condition as % of C_1		100	75	56		100	80	72		100	72	61		100	31	19

P denotes patient s reference number C_1 denotes patient s initial condition, C_2 his condition 4 weeks later, and C_3 his condition after treatment for 8 weeks

C_1, C_2, C_3 denote the corresponding averages

Details for the 2 cases with bilateral effusions are

P		C_1	C_2	C_3	Treatment
2	L. lung	4	1	1	P
	R. lung	0	3	0	
77	L. lung	1	0	0	V
	R lung	3½	2½	2½	

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* Each tablet contained thiamine chloride 3 mg , riboflavin 2 mg , nicotinamide 20 mg , calcium pantothenate 1 mg , pyridoxin hydrochloride 0·25 mg

TABLE IV—PROPORTION OF COMPLETE RESOLUTIONS

Treatment	No of patients	First 4 weeks			All 8 weeks		
		Cures	% cures	95% confidence interval	Cures	% cures	95% confidence interval
V, P, and T (combined)	53	6	11·3%	4·3% to 23·4%	8	15·1%	6·7% to 27·6%
TS	20	9	45·0%	23·1% to 68·5%	12	60·0%	36·1% to 80·9%
TS minus V, P, and T (combined)			33·7%	9·9% to 57·5%		44·9%	20·9% to 68·9%

The superiority of treatment TS is demonstrated in another way in table IV in which results are judged, not on the relative degrees of absorption of fluid as in table II, but on whether complete resolution of the effusion had occurred or not during the whole of the 8 weeks of the study Because of the similarity of results in groups V, P, and T, these were combined and compared with group TS Analysed in this way 12 out of the 20 cases in group TS resolved completely compared with 8 out of 53 in the remaining 3 groups (2 out of 18 in V, 2 out of 16 in P, 4 out of 19 in T) This difference is again highly significant.

Within each treatment group no significant statistical differences were found between the behaviour of those with hæmorrhagic and those with serous effusions

Discussion

Because of certain administrative difficulties it was unfortunately not possible to prolong the trial beyond 8 weeks Even in this short period, however, definite conclusions were reached with regard to the relative values of treatments V, P, T, and TS

It may be inferred from the failure of ascorbic acid to hasten the clearing of the fluid that scurvy is not an important ætiological factor in the cases studied Those receiving penicillin fared no better There was no reason to believe that any patient entering the trial was suffering from, or had recently suffered from pneumonia, and the absence of response to penicillin was additional evidence against this possibility Results with the tetracyclines might have been better, but the inclusion of such a group was not practicable

The group which received streptomycin and isoniazid showed no advantage over groups V or P Although the patients participating in this trial were regarded, for reasons mentioned earlier, as suffering in all probability from effusions of tuberculous origin, this seemingly paradoxical response was not unexpected in view of previous findings In a controlled study, Emerson (1955) showed that whereas antituberculous therapy markedly diminished the incidence of subsequent frank tuberculosis, it had no appreciable effect on the actual resolution of the pleural fluid This conclusion was confirmed by Forgacs (1957) It is suggested that what improvement did occur in groups V, P, and T was due in each instance to natural remission

The addition of adrenal steroids to the streptomycin and isoniazid resulted in a striking reduction in the amount of pleural fluid, and in most instances within the first 4 weeks of treatment The benefit of treatment TS is evident when comparing not only the rate of clearing of the fluid but also the final proportion of complete resolutions The fact that improvement in this group was significant in the first 4 weeks but not in the second can be explained on the grounds that after the initial beneficial effect there was little room for further improvement. The superiority of this form of treatment is probably due to the effect of corticosteroids on the allergic component of the disease (Paterson 1917, Petroff and Stewart 1925, Howard and de Veere 1936, Rich 1946), but the use of this drug alone would clearly be inadvisable for fear of reactivating an underlying tuberculous process

The manner in which treatment TS rapidly controlled the constitutional disturbance in seriously ill patients was impressive, pain, fever, and malaise usually disappeared within a few days of starting treatment This was particularly noteworthy in the 4 patients receiving treatment V or P who were removed from the trial on account of marked deterioration and given treatment TS

In 1 of them (originally on treatment V) considerable deterioration was accompanied by the appearance of ascites, and institution of treatment TS resulted in rapid improvement with disappearance of the peritoneal fluid within 5 days It is recognised that the withdrawal of these 4 cases affects the random character of the trial to some extent, but in our judgment it was essential to do so as their lives appeared to be in jeopardy If anything, the withdrawal of these cases lessened the statistical advantage of group TS to some extent

The clinical response to treatment T was also noticeably superior to that of treatments V and P, although not to the same extent as treatment TS

Also of interest is the fact that a number of patients (not connected with the trial) with pericardial and peritoneal effusions of presumably tuberculous origin, were given treatment TS with equally beneficial results

It is a matter for regret that since these patients were migrant labourers a comprehensive follow-up study could not be carried out.

Summary and Conclusions

A therapeutic trial was designed to evaluate 4 different methods of treatment of pleurisy with effusion in African labourers employed in the goldmining industry on the Witwatersrand The treatments were (*a*) standard antituberculous treatment, (*b*) standard antituberculous treatment with the addition of adrenal steroids, (*c*) ascorbic acid, and (*d*) penicillin

Antituberculous drugs combined with adrenal steroids proved to be much superior to the other methods

Scurvy and pneumonia do not appear to be significant ætiological factors in pleural effusions occurring in this population

Our thanks are due to Dr I Webster, of the Pneumoconiosis Research Unit of the South African Council for Scientific and Industrial Research, for performing the investigations on the pleural fluid, and to the South African Institute for Medical Research for the other laboratory investigations We are grateful to The Upjohn Company for the generous donation of 'Deltacortef'

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SEVERE HYPERSENSITIVITY TO SULPHAMETHOXYPYRIDAZINE

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In the case described here the patient showed extreme hypersensitivity to sulphamethoxypyridazine, a long-acting sulphonamide preparation

Case-report

A married woman, aged 41, had for fourteen years had rheumatoid arthritis, for which over the past two years she had been having small daily doses of cortisone In November, 1958, because of a productive cough and lassitude she was seen at a chest clinic and was thought to have tuberculosis While investigations were continuing, a course of oxytetracycline, to be followed by a course of sulphamethoxypyridazine ('Lederkyn') 0 5 g daily, was prescribed.

After the patient had taken 3 g of this sulphonamide, a generalised erythematous rash developed Her doctor was called in and promethazine hydrochloride tablets were prescribed. As the irritation persisted she was admitted to hospital

Examination and Treatment

On admission the patient was pyrexial, there were physical signs of bronchitis, and she had a generalised urticarial rash with severe œdema of the face She was considered to have a drug sensitivity reaction and the promethazine hydrochloride was continued Next day the urticaria had progressed to vesiculation, later the vesicles coalesced so that the entire skin surface of the body, apart from the scalp, was converted into a fluid sac Promethazine hydrochloride was discontinued and prednisone started immediately, 60 mg was given in the first twenty-four hours, and subsequently 40 mg daily until the drug was "tailed off"

A chest X-ray revealed right basal pneumonia, and erythromycin was started in view of the finding of pneumococci in the sputum culture Later, because of changes in the flora, she was given courses of chloramphenicol and tetracycline

Management

Although the patient's general condition was very poor, an adequate intake of fluids was maintained orally, the serum-proteins and electrolytes on repeated estimations remained within normal limits The question of transfusion of plasma and/or fresh whole blood was raised, but, because of the congestion of the lungs and the danger of pulmonary œdema, action was delayed.

Nursing became more difficult as the entire skin surface peeled off, leaving only raw dermis, the mucous membranes of the mouth and tongue also sloughed off

A 'Ripple' bed, as used for poliomyelitis, was obtained Non-greasy tulle-gras dressings were considered necessary for nursing and handling this patient, the problem was how to apply and maintain such extensive dressings The condition of the lungs in such a gravely ill patient precluded general anæsthesia or even basal narcosis It was therefore decided to attempt to produce analgesia and, if possible, amnesia by hypnosis

The patient proved an excellent subject, possibly because she was in a state of shock She rapidly reached a deep somnambulistic level, and surface analgesia was obtained. She was moved to the theatre and full dressings were applied, catatonia, which is usual in deep hypnosis, proved most valuable for limb dressings, the patient maintaining her limbs upright and unsupported indefinitely The theatre sessions proved lengthy (approximately one and a half hours) but the patient's condition remained good throughout these periods

After four days of prednisone, corticotrophin 40 I U was given daily in addition, as the exudative process was not completely under control.

Progress

On the eleventh day the patient showed some signs of improvement and, although the tongue and buccal mucous membranes were still raw (despite mixed supplementary vitamins), she could eat puréed foods, but it was not until two or three days later that the ultimate prognosis seemed more hopeful On the seventeenth day a chest X-ray showed that the lung fields had cleared

The more deeply affected areas on the buttocks and thighs could now be treated by exposure to the air and new skin and nails gradually grew The scalp being unaffected, there was no loss of hair The skin, which had completely regenerated in six weeks, was extensively and deeply pigmented.

The prednisone was "tailed off" and discontinued after seven weeks, and the corticotrophin was stopped a week later, without any upset.

Tests for Sensitivity

Skin tests with all the drugs the patient had taken before admission were negative These drugs were then given orally in small test doses (quarter normal dose)

Six hours after the patient was given 125 mg of sulphamethoxypyridazine she felt her joints becoming stiff and painful, her temperature rose, and her face became flushed and œdematous She was immediately given 40 I U corticotrophin and 20 mg prednisone When, after eighteen hours, symptoms subsided the steroids were slowly withdrawn

The other drugs were given in test doses without any reaction and the patient was discharged after three months with new nails and a new skin (the pigmentation fading gradually) Although there were no arthritic symptoms, the latex fixation test was positive

A "pink card" was given to this patient stating that she had had corticosteroids and that she was hypersensitive to long-acting sulphonamides The patient's impatience to go home precluded desensitisation to the offending drug

Discussion

Sulphamethoxypyridazine is reported to be as effective as sulphadiazine (Terrell et al 1957), and, because of its very slow renal excretion, adequate blood-levels are maintained for long periods on relatively small doses Side-reactions are slight and uncommon Vinnicombe (1958) reported that no serious sensitivity reaction had been reported

Davis and Tachjian (1956) reported an extremely severe general reaction to sulphafurazole which had many of the features of our case, and which also required intensive treatment with steroids and antibiotics A less severe reaction to sulphadimidine (Fox 1955) started after five days' treatment and ended with pigmentation of the skin at the sites of the original bullous lesions

In our patient the recently discontinued steroid therapy probably increased the severity of the reaction The use of hypnosis in the management of this patient is of interest since this case resembled in many ways one of extensive second-degree burns Bayles (1959) has advocated the more general use of hypnosis in cases of severe burns The advantages of a deep trance state over general anæsthesia are that the patient remains fully cooperative, the cough reflex is retained, while analgesia and amnesia for dressing sessions are assured

We should like to express our admiration of Sister S Jarrett and her staff whose patient and tireless nursing played a major part in the recovery of this patient

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RENAL HÆMODYNAMICS IN HEPATIC CIRRHOSIS

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FACTORS such as diminished osmotic pressure of plasma and raised portal pressure are known to be insufficient to explain the œdema and ascites of hepatic cirrhosis Recent views have given a special importance to adrenocortical steroids and renal factors, and we have studied changes in renal hæmodynamics in patients with cirrhosis

In 17 cirrhotics the following were studied (*a*) glomerular filtration-rate (G F.R), (*b*) renal plasma flow (R P F), (*c*) renal reabsorption of sodium, and (*d*) daily urinary excretion of total formaldehydogenic steroids

15 of these 17 patients were men and 2 were women 3 normal persons were also studied for comparison The investigation continued for from 20 to 40 days and was divided into two periods during the first the patients and controls had a diet in which 6 g of sodium chloride was added daily to their standard high-protein low-fat diets for at least 7 days During the second period the patients and the normals returned to a low-salt regime During both periods all five observations mentioned above were studied.

According to the clinical picture, the 17 patients were divided into two groups (*a*) progressive and decompensated (12), and (*b*) regressive (5)

We measured G F R with mannitol, and R.P F with *p*-aminohippurate (Page and Corcoran 1949) Both were given into a vein in continuous saline infusion throughout the examinations Sodium was measured in urine and plasma by uranyl acetate (Hinsberg and Lang 1951) Total formaldehydogenic steroids in the urine were estimated by a modification of the periodic-acid oxidation method (Rivoire and Paszkowski 1952)

PRINCIPAL FINDINGS IN 12 PROGRESSIVE DECOMPENSATED CASES OF CIRRHOSIS

Case		G F.R.	R.P.F	Sodium clearance (%)	F S mg per/day	F.F	Ascites
1	E.S	65	288		0 88	0 22	+++
	L.S	36	144	0 30		0 25	
2	E S	77	520		2 00	0 14	+++
	L.S	64	356	0 70		0 18	
3	E.S	40	160	0 69	3 50	0 25	+++
	L.S	41	201	0 81	4 90	0 20	
4	E.S	45	140			0 32	+++
5	E S	36	252	0 50	2 10	0 14	++
	L.S	34	267			0 12	
6	E.S	80	275	0 36	0 80	0 29	+++
	L.S	90	255	0 28	1 90	0 36	
7	E.S	41	187	0 33	2 25	0 21	++
8	E.S	68	250	0 87	1 80	0 27	+++
	L.S	64	320		2·40	0 20	
9	E.S	30	170		0·46	0 17	+++
10	E S	109	500	0 26	2 30	0 21	+++
	L.S	131	608	0 15	1 75	0 20	
11	L.S.	100	580	0 95	3 00	0 17	+++
	L.S	90	503	1 00	1 00	0 16	
12	E S	120	385	1 00	1 30	0 30	+++
	L.S	140	415	0 27		0 30	

PRINCIPAL FINDINGS IN 5 REGRESSIVE CASES OF CIRRHOSIS

13	E.S.	97	444	1 9	1 9	0 20	+
	L.S	98	579	0 5	0 8	0 18	
14	E.S.	174	887	1 8	1 6	0 19	+
	L.S	95	724			0 13	
15	E S	45	216	1·4	1 1	0 20	+
	L.S	95	570	0 3	2 6	0 16	
16	E.S	78	485	1 6	2 8	0 16	+
17	E S	110	500	0 4	3 5	0 20	+
	L.S	180	550	1 3	3 3	0 30	

E.S = extra salt.
L.S = low salt
G F R glomerular filtration rate (ml per min)
R P.F = renal plasma flow (ml per min)
F.S. = formal dehydogenic steroids (mg per day)
F F = filtration fraction.

In cases 4 7, 9, and 16 it was not possible to have a low-salt period

Results

(*a*) In 9 of the 12 cases in the first group, we found obviously low values for G F (56 5 ml per min.) and R.P F (249 ml per min.) Filtration fraction (F F) was 0 22 in this group According to these values, G F and R.P F were reduced to less than half normal In the other 3 cases the G F and R P F were normal or slightly reduced Enormous ascites was present in these 3 cases, which suggests that ascites plays little part in decreasing the renal circulation

In the first group, the renal excretion of sodium was strikingly low (0 53% of filtered sodium)

(*b*) Results in the second group were mean values for G F and R.P F 101 ml per min. and 535 ml per min. respectively, F F 0 18, renal excretion of sodium 1 1%

Renal hæmodynamic values were more or less the same during both low-salt and extra-salt periods in cirrhotics

(*c*) The values for total formaldehydogenic steroids in urine were normal or slightly low in both groups (1 83 mg per day in the first and 2 2 mg per day in the second) The data are shown in the tables

DISCUSSION

The results of different investigators who have studied this subject do not all agree In 3 cases with ascites Patek et al (1948) found normal values for G F Goodyer et al (1950) also observed normal values for G F in 4 out of 5 cirrhotics, and Epstein et al (1950) recorded normal values for G F in cirrhotics On the other hand, Leslie et al (1951) found low values for G F and R P F in cirrhotics with considerable ascites and œdema

These striking differences suggest that renal hæmodynamic changes are important in fluid accumulation in cirrhosis In the cases with low hæmodynamic values, sodium clearances and total daily renal sodium excretion were significantly lower than when the renal hæmodynamic values were normal It seems reasonable to say that renal circulatory insufficiency and defects in renal salt excretion run parallel, and that is a definite finding in decompensated cases

The connection between low G F and diminished salt excretion was demonstrated by Merrill (1946) in congestive cardiac failure, and confirmed by others We also recorded similar findings, particularly very high F F values, in congestive heart-failure (Önen 1951), and we emphasised the importance of high F F values and the consequent high osmotic pressures in the efferent arterioles It seems logical that excessive reabsorption of sodium also takes place in hepatic cirrhosis, at least in its later stages

The causes of this " renal hæmodynamic insufficiency " are debatable At first sight ascites could be taken as a cause of decreased G F and R P F , but neither clinical nor experimental observations support this Results in 3 cases in the first group and all in the second group with ascites make this possibility unlikely

We could not measure aldosterone excretion in the urine Apart from aldosterone's effects on salt excretion, the diminution of G F and R P F may reduce renal clearance of aldosterone itself, and it would seem logical, therefore, to estimate the plasma-aldosterone as well in cirrhosis

SUMMARY

Renal hæmodynamics were studied in 17 cases of portal cirrhosis In 12 progressive and severely decompensated cases hæmodynamic figures were strikingly low On the other hand, in 5 mild and regressive types of cirrhosis, glomerular filtration-rate and renal plasma flow were normal

Total urinary formaldehydogenic steroids were normal or slightly reduced in both groups

The possible role of renal hæmodynamics in salt and water retention in cirrhosis are briefly discussed

I am indebted to Prof Dr Sedat Tavat, director of the department of therapeutics and pharmacology, and Prof N Kastarlak, Prof R Garan, and Prof S Artunkal for their valuable suggestions and kind help

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HYPOGLYCÆMIA ASSOCIATED WITH RETROPERITONEAL LEIOMYOSARCOMA

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HYPOGLYCÆMIA associated with fibrosarcomata and sarcomata is rare, and only 8 examples have been reported (Doege 1930, Seckel 1939, Arkles 1942, Hines 1943, Skillern et al 1954, Silvis and Simon 1956, Holton 1957) The case described here is believed to be the first recorded in Britain

Case-report

A married woman, aged 56, para. 3, was admitted to a medical ward of the Aberdeen Royal Infirmary on Oct. 1, 1957 Thirteen days previously she had been found unconscious in bed and had then been admitted to the local cottage hospital Spells of unconsciousness had continued after admission and had become longer in duration before her transfer to Aberdeen.

Her previous medical history had been uneventful, apart from rheumatic fever at the age of 26 She had been breathless on exertion for a few months, and about five weeks before admission to hospital began to have attacks of nocturnal sweating, which usually wakened her at about 4 A M , these passed off spontaneously, and she felt well during the day and was able to do her housework. She had noticed her abdomen becoming larger during the previous two months and did not think she had become thinner

Soon after admission, while being examined she became very drowsy and fell asleep She was rather obese The heart and lungs seemed normal The pulse-rate was 88 and the blood-pressure 200/95 m.m Hg There was moderate sacral and ankle œdema The urine was sugar-free and seemed normal in other respects A large, fixed, irregular, hard mass which was not tender filled the pelvis and the lower abdomen up to the umbilicus Although there was no obvious ascites malignant ovarian tumour was provisionally diagnosed.

Two hours after admission the patient became very restless and confused, and sweated profusely Paradehyde 8 ml. and phenobarbitone sodium gr 3 were given by intramuscular injection. On the following day at 1 P M the blood-sugar content was found to be 37 mg per 100 ml 50 ml of 50% dextrose solution was given intravenously, and the patient immediately regained consciousness for the first time since her initial examination. Repeated blood-sugar examinations confirmed that the unconsciousness was due to hypoglycæmia, which could be controlled by intravenous and oral glucose Electrocardiography examination showed myocardial changes which were thought to be due to the hypoglycæmia.

Other laboratory investigations gave the following results hæmoglobin 83% (12 3 g per 100 ml. Eel electric colorimeter 100% = 14 6 g per 100 ml.), white blood-cells 8000 per c.mm., plasma-CO_2 64 vols % (22 7 mEq per litre), serum-potassium 10 9 mg per 100 ml. (2 8 mEq per litre), serum sodium 325 mg per 100 ml (141 4 mEq per litre), serum-chloride 600 mg per 100 ml (103 mEq per litre), serum-phosphate 2 9 mg per 100 ml. (1 68 mEq per litre), cerebrospinal fluid protein 30 mg per 100 ml , cells none, Wassermann reaction negative, Thymol turbidity 2 units, serum-alkaline-phosphatase 13 5 King-Armstrong units, serum-bilirubin 0 3 mg per 100 ml.

Two conditions were considered as possible causes of the hypoglycæmia (1) islet-cell tumour of the pancreas, and (2) fibroma or sarcoma causing hypoglycæmia (Conn and Seltzer 1955) It was decided to perform laparotomy on Oct 7, 1957

Preparation for Operation

In order to prevent hypoglycæmia during the operation a cardiac catheter was inserted into the superior vena cava the evening before the operation, and 2 pints of 50% dextrose solution was infused in the next twelve hours The blood sugar level was maintained at about 190 mg per 100 ml

Conn and Seltzer (1955) recommended administration of the corticotrophin to prevent the "idiopathic hyperthermia" which caused 5 out of 18 postoperative deaths in a series of cases reported by Howard et al (1950) 50 units of aqueous corticotrophin was therefore given eight-hourly for twenty-four hours before operation.

Operation

A large retroperitoneal tumour was found. It seemed to originate and be fixed to the area of the right pubic ramus, and extended medially between the bladder and the uterus, the latter being normal in size and behind and below the tumour Both fallopian tubes and ovaries were normal

A line of cleavage was found in the capsule of the tumour and the mass was enucleated. The tumour was very vascular, and considerable bleeding occurred. The mass was very adherent to the bladder, and while it was being separated a small hole was torn in the bladder wall, this was repaired in the usual manner In order to control the bleeding subtotal hysterectomy was also performed The raw area, left after removal of the tumour, was covered with peritoneum and a drain inserted into the pouch of Douglas

The liver was normal to palpation, but a small hard nodule was felt in the pancreas where it crossed the aorta. This was not considered to be significant. The drain from the pouch of Douglas was brought out through the abdominal incision, which was then closed A self-retaining catheter was inserted into the bladder

Postoperative Course

3 pints of blood was given during and after the operation and followed by intravenous saline solution at a slow rate of flow Blood-sugar estimations were performed hourly during the first day and thereafter at longer intervals The blood-sugar level remained within normal limits, no additional glucose being required On the second postoperative day the intravenous infusion was stopped and fluids were given by mouth The serum-potassium was 10 0 mg per 100 ml (2 5 mEq per litre) on the second day after operation, and therefore 1 g potassium chloride in 1 oz fruit juice was given four-hourly till the seventh day when the serum-potassium was 20 mg per 100 ml. (5 mEq per litre) In view of the malignancy of the tumour the chest was X-rayed, but no metastases were detected. A course of deep X-ray therapy was given to the pelvis, and the patient was discharged from hospital on Nov 13, 1957 When last seen, in February, 1959, she was very well, with no symptoms of hypoglycæmia and no evidence of recurrence of the tumour A mid-day blood-sugar estimation showed the level to be 85 mg per 100 ml.

Pathological Report

The tumour mass measured 10 in. × 7 in. × 4½ in. (25 4 cm. × 17 7 cm. × 10 4 cm.) and weighed 2750 g

Histology (Prof J S Young)—" The tumour presents the histological characteristics of a sarcoma. The predominant tumour cell is elongated and possesses a vesicular nucleus which is rod-shaped with rounded ends Throughout the section oval or spheroidal cells, always with vesicular nuclei, are observed, but it may be inferred that such variations in shape are attributable to the different planes of section in which the cells have been cut. In particular there is no reason to suspect that the spheroidal cells are neoplastic epithelial cells Mitoses are present but they are so relatively scanty as to suggest that the grade of malignancy is likely to be low In several of the sections it is evident that the tumour is invested by a substantial fibrous capsule With regard to its histogenesis the growth is most probably a leiomyosarcoma despite the fact that neither fasciculation nor pleomorphism of the tumour cells is a conspicuous feature "

Discussion

Several types of large tumours in various sites are known to produce hypoglycæmia

Four adrenal tumours associated with hypoglycæmia have been reported (Anderson 1930, Lawrence 1937, Broster and Patterson 1948, Staffieri et al 1949) Three of these tumours appeared to arise in the adrenal cortex, and microscopically the cells were similar to those seen in adrenocortical carcinoma. The case reported by Lawrence had, in addition to hypoglycæmia, features suggestive of Cushing's syndrome, and that reported by Broster and Patterson had marked virilism. The hypoglycæmia in these cases may have been due to adrenal failure or to a substance secreted by the tumour

Three patients had sarcomatous tumours in the thoracic cavity (Arkles 1942, Doege 1930, Skillern et al. 1954) One had a fibromatous tumour of the liver causing hypoglycæmia (Seckel 1939) The remaining reports are of sarcomatous or fibrosarcomatous tumours situated in the abdomen (Hines 1943, Silvis and Simon 1956, Skillern et al. 1954, Holton 1957) These abdominal tumours were all situated in the upper abdomen, whereas in our case the tumour originated from the pelvis

When the tumours are removed surgically the hypoglycæmia disappears, to return if the tumour recurs In the case reported by Arkles (1942) the tumour recurred after seven years, and this resulted in a return of the hypoglycæmia and death, in Hines' (1943) case recurred after two years, with metastases and hypoglycæmia, in Holton's (1957) case the interval between operation and recurrence with death from hypoglycæmia was five years In the other reported cases insufficient time had elapsed for the final outcome to be known On the whole it seems that the degree of malignancy in these tumours is usually low, so recurrence is delayed for some years and in the interval the patient remains well Microscopically the tumours are mainly sarcomata with round and/or spindle cells

Those occurring in the adrenal gland, which are really a different entity, are similar to those found in adrenal carcinoma Skillern et al (1954) found blue-staining beta granules in the cytoplasm of the occasional round cell in one of their cases They considered these to be insulin-secreting, similar to these found in the pancreas

The main problem posed by these tumours is the cause of the hypoglycæmia Four main hypotheses have been put forward

1 These tumours secrete insulin or some other substance which lowers the blood-sugar level. Seckel (1939) and Howard et al. (1950) performed insulin assay of the tumours in their cases but found none Although insulin assays were not performed on their cases, Skillern et al (1954) believed that the diagnosis of insulin-producing neoplasm was justified by the demonstration in one of their cases of round cells resembling the beta cells of the pancreas, the demonstration of blue-staining granules in an occasional round cell in the tumour of their second patient, and the complete relief of hypoglycæmia by extirpation of the tumour

Without insulin assay it is not possible to say whether the tumours produce insulin or not No beta granules were found in the tumour cells of our case Possibly the spindle cells may have originated from ectopic pancreatic islet tissue, but this cannot be proved.

2 The tumour utilises glucose excessively, thus causing hypoglycæmia This seems a possible explanation, but many patients with large tumours histologically similar to the case reported do not have hypoglycæmia. Increased uptake of glucose by the tumour would account for the low serum-potassium levels preoperatively in this case, the potassium migrating into the cells with the glucose

Woodward and Fry (1932), however, found that tumour tissue can glycolyse carbohydrate more rapidly than normal tissue and that the blood-sugar level is raised in cases of cancer It might be assumed that a rapidly growing neoplasm induces increased glycogenolysis, thus elevating the blood-sugar as long as stores are not depleted. When stores of glycogen are used up hypoglycæmia might ensue

3 Coincident presence of a pancreatic adenoma causes the hypoglycæmia This was ruled out in the present case, although at operation a small hard nodule was felt in the pancreas where the gland crosses the aorta. Before the pedicle of the large tumour was clamped a blood-sugar reading was 250 mg per 100 ml Forty minutes after clamping, and while intravenous glucose 50% was still being administered, the blood-sugar rose by 86 mg per 100 ml. It was therefore considered that the large tumour had been causing the hypoglycæmia. This valuable method of assessing the effect of removal of the tumour on the blood-sugar before closing the abdomen was suggested by McMillan and Sheibe (1951) A pancreatic adenoma could finally be excluded in this case by the patient's subsequent progress

4 The hypoglycæmia is due to stretching or disruptive effects of unknown receptors in the abdomen. Evans et al (1931) showed in the cat that disruption of the sympathetic nerve-supply to the liver causes hypoglycæmia Rosenfield (1949) postulated, in a case of pseudomyxoma peritonei with hypoglycæmia, that, since large amounts of tumour mass were present in the area of the cœliac ganglion and the right splanchnic chain, the hypoglycæmia might be due to interference with the sympathetic nervous system.

The diversity of pathological picture in the reported cases is against the hypothesis that the tumours produce insulin or an insulin-like substance The cause of the hypoglycæmia must necessarily be in doubt until insulin assays have been more widely performed

We wish to thank Prof Dugald Baird and Dr R J Duthie for permission to publish this case and for helpful advice, Prof J S Young for the histological report, and Mr A W Wilkinson for his help in the management of the patient

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Preliminary Communications

TRETAMINE IN THE TREATMENT OF INOPERABLE LUNG CANCER

THE first use of tretamine (2 4 6-triethyleneimino-s-triazine, triethylene melamine [T E M]) in the control of clinical malignancy[1] followed its release for research purposes by Imperial Chemical Industries as the result of observations[2 3] on the inhibitory action of this and related compounds on the growth of experimental tumours Other clinical reports[4] followed independent parallel discoveries made at the Sloan-Kettering Research Institute, New York

Experimental work on mice[5] showed that tretamine had very considerable activity against sarcoma 180 and lymphosarcoma L 1 The best response was obtained by large doses at infrequent intervals

In 15 cases of lung cancer treated with this drug[6] 4 showed marked clinical improvement but no radiological change In this and most subsequent reports the method of dosage has been frequent small doses over a period of a few weeks Most workers have found it to be very toxic on the hæmopoietic tissues when so used Wilkinson[7] regarded it as the mos toxic of all agents he had tried.

During the period July to November, 1959, 43 patients with advanced inoperable lung cancer have been treated with tretamine Untreated the majority of these patients would have been dead within three months and many earlier than this After some experiment a pattern of dosage that has given very encouraging results has been worked out 30 patients have shown subjective improvement and in 10 of these very marked to complete regression of the tumour has occurred

In 4 cases the chest X-ray has returned to normal or near normal and it is these 4 results that have stimulated this preliminary report Radiologically each patient had a large mass at one or other lung root with considerable enlargement of the superior mediastinal shadows Tumour tissue was obtained from the bronchi or from neck glands or from both sites and in each instance was reported as an undifferentiated carcinoma *Additional details are given in the table and* X-rays representative of the series are shown in figs 1 and 2

Treatment of these 4 cases consisted of one or two large doses of tretamine given intravenously, with a total dose of 15 to 30 mg This dose may be followed by severe nausea for twenty-four hours Within three days subjective improvement was evident, and chest X-ray done routinely on the fifth day showed evident shrinkage of the tumour mass This shrinkage continued over the next three weeks and at the end of a month the chest X-ray had returned to normal

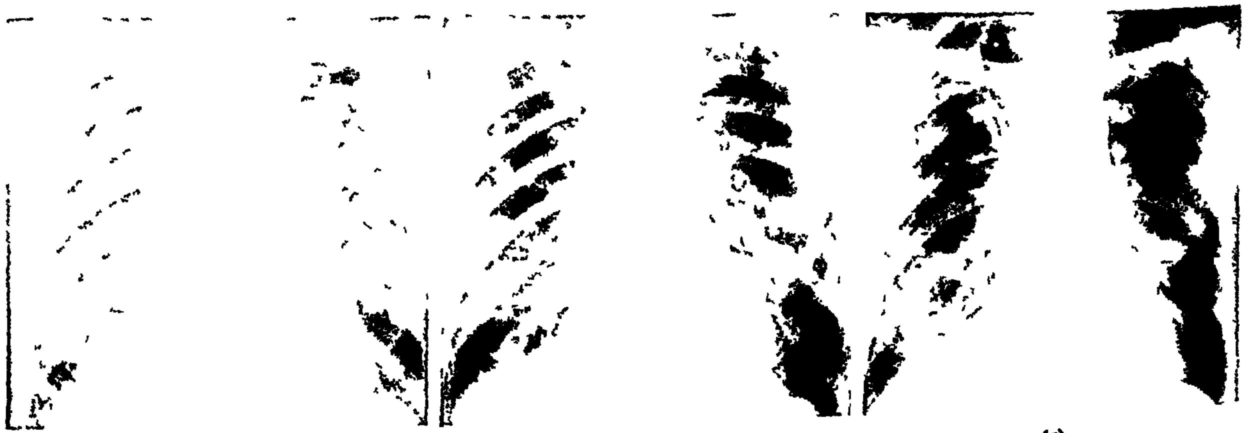
(a) (b) (c)

Fig 1—Case 1 (a) X-ray one month *before start of treatment, thereafter* the patient was bed-ridden and portable films were unsatisfactory (b) one month after treatment, (c) three months after treatment

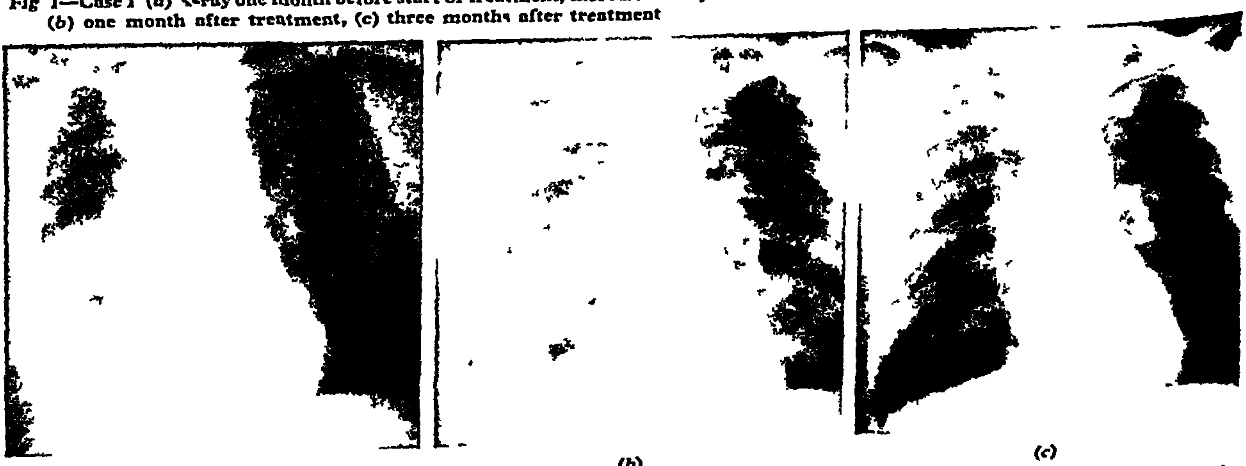
(a) (b) (c)

Fig 2—Case 2 (a) Day before treatment, (b) five days after 30 mg tretamine, the chest was not aspirated and no other treatment was given, (c) one month later

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[1] Paterson, E , Boland, J *Brit J Cancer*, 1951, 5, 28

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[5] Goldberg, B , Schoenbach, E B *Cancer*, 1951, 4, 1125

[6] Saline, M , Baum, G L *J Amer med Ass* 1954, 156, 1493

[7] Wilkinson, J F *Proc R Soc Med* 1953, 46, 685

DETAILS OF 4 CASES OF INOPERABLE BRONCHIAL CARCINOMA TREATED WITH TRETAMINE

Case	Age (yr.)	Sex	Dose of tretamine	Lowest white count (per c.mm.)	Lowest platelet-count (per c.mm.)	Clinical features	Result
1	67	M	10 mg 10 mg	1700 –	69,000	Left hilar shadow Left recurrent nerve palsy Bed-ridden by weakness Stridor	X-ray normal at one month Voice normal at three months when still completely well
2	53	M	30 mg	840	25,000	Superior vena caval obstruction Dysphagia Bilateral neck glands Secondary in 7th thoracic vertebra	X-rays normal at one month except for translucency in vertebra
3	62	M	30 mg	1200	10,000	Stridor Early superior vena caval obstruction. Gross œsophageal distortion Large mass left hilum	X-rays normal at three weeks
4	57	M	30 mg	500	12,000	Complete collapse left lung Left hilar mass Slight stridor	X-ray normal at one month

Of the other 6 patients whose tumours have undergone marked regression, 3 died within twelve days after the start of treatment, owing to hæmorrhage from the tumour which had undergone necrosis, the platelet-count was at a safe level at the time of these hæmorrhages

The remaining patients were treated because of metastases from bronchial tumours previously removed. Only a clinical assessment of the regression of these metastases could be made since they were not radiologically visible. The patients, however, are all well and symptomless and the follow-up results are awaited.

In every case there has been a depression of the white blood-cells and the platelets The white blood-count falls to its lowest level about the twelfth day and if below 500 at this time prednisolone and penicillin have been given for a period of seven to ten days. The platelet-count has been more variable and usually reaches its lowest point about the fifteenth day In 2 patients a slight purpuric rash occurred with a platelet-count of less than 25,000 per c.mm. Both were given a transfusion of fresh blood. Some of the early cases were treated with repeated small doses of tretamine, in 3 of these severe purpura occurred and blood-transfusion was urgently needed. It is considered advisable to watch very carefully for evidence of purpura from the twelfth day onwards It was found expedient to do blood and platelet counts on alternate days until a moderate pancytopenia was present and then daily until the counts had returned to near normal

Pyridoxine (100 mg intramuscularly once daily) and dimenhydrinate ('Dramamine') (50 mg six-hourly) has been given four hours after tretamine to control the nausea which occurs on the first day of treatment, and 'Villescon' (two tablets twice daily) has helped to restore a more than normal appetite by the fifth day of treatment.

Tretamine in a single dose of 20–30 mg (0·35 mg per kg) intravenously should be tried in inoperable undifferentiated cancer of the lung The pancytopenia is manageable with prednisolone and penicillin and occasionally blood-transfusion We do not yet know the duration of remission that this will produce nor have we any information on the effects of a second course of treatment The problem of hæmorrhage from necrotic tumour needs to be solved, and the possible place of this drug in combination with surgical excision must also be considered.

We should like to acknowledge with thanks generous supplies of tretamine provided for this investigation by Imperial Chemical Industries Ltd, and much useful information from Dr A L. Walpole, of I C I Research Laboratories.

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SERUM-5-HYDROXYTRYPTAMINE LEVELS FOLLOWING EXPERIMENTAL INCREASE IN GASTROINTESTINAL ACTIVITY IN MAN

THERE are good reasons for believing that much of the blood-5-hydroxytryptamine (5-H T) is derived from the enterochromaffin cells of the gastrointestinal tract Haverback and Davidson [1] have demonstrated low levels in a patient with extensive resection of large and small bowel By means of a cardiac catheter, Erspamer and Testini [2] found more 5-H T in the hepatic vein than in the inferior vena cava of patients Experiments on the guineapig intestine [3] have shown that increased intraluminal pressure releases 5-H T from the gut, and Kowlessar et al [4] have reported an increase in the excretory product of 5-H T in the urine of patients with diarrhœa due to non-tropical sprue It is possible, therefore, that 5-H T has some role in maintaining the motility of the intestine and that during increased small-bowel activity a larger quantity is released into the circulation The following experiments were conducted to test this hypothesis

METHODS

Volunteers were obtained from a group of healthy medical students Serum-5-H T was extracted by the method of Hardisty and Stacey [5] The extracts were assayed on rat uteri

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1 Haverback, B J, Davidson J D *Gastroenterology* 1958, 35, 570
2. Erspamer, V, Testini, A *J Pharm, Lond* 1959, 11, 618
3 Bulbring, E., Crema, A. *J Physiol* 1959, 146 18
4 Kowlessar O D Williams, R C., Law, D H, Sleisinger, M. H *New Engl J Med* 1958, 259 340
5 Hardisty R M, Stacey, R S *J Physiol* 1955, 130, 711

EFFECTS OF ADMINISTRATION OF CARBACHOL AND MAGNESIUM SULPHATE TO VOLUNTEERS

Treatment	No of subjects	No of abdominal sounds per min. (mean ± S.E)		Serum-5-H.T (µg per litre) (mean ± S.E.)		Mean of differences in serum-5-H.T (µg per Litre) (mean ± S.E)	Significance of mean difference (P)
		Before treatment	After treatment	Before treatment	After treatment		
Carbachol 0 2 mg subcutaneously	5	7 ± 3	69 ± 17	139 ± 1·6	182 ± 12 5	43 ± 10 8	0·02
Magnesium sulphate 30 g orally	5	5 ± 1 3	47 ± 26	184 ± 25 3	202 ± 21	18 ± 0·4	0·02
Exercise (350 kg per min. for 15 min.)	5			180 ± 32	175 ± 39	−5 ± 152	0 8

pretreated with stilbœstrol, using automatic apparatus (Casella electronics) adapted for superfusion Immediately after withdrawing the first blood sample from the volunteer, carbachol 0 2 mg was injected subcutaneously, or magnesium sulphate 30 g in 250 ml water was ingested orally Increased motility of the bowel was estimated by recording on tape the noises produced by the intestine, a conventional tape-recorder was employed with its microphone suitably protected from extraneous sounds and applied to the abdominal wall. The electrical output of the tape was amplified and the pulses were then counted on a scaler This method is similar to that used by Farrar and Ingelfinger [6] The second blood sample was taken one hour after the injection of carbachol and four hours after the ingestion of magnesium sulphate Three or four four-point assays were performed on each blood sample

RESULTS

The results are summarised in the accompanying table Fifteen subjects were studied Of five treated with carbachol, all showed an increase in the serum-5-H T The mean increase was 43 µg per litre and was significant at the 2% level of probability The five subjects who ingested magnesium sulphate (30 g) showed less increase in motility and a smaller rise in 5-H T of 18 µg per litre, which was still large enough to be significant at the same level of probability The changes in serum-5-H T are not simply due to repeated blood sampling as is shown by the control subjects, who received no intestinal stimulant but instead took a short period of exercise between the two blood samples In these subjects there was no significant difference between the 5-H T levels in the first and second samples, indicating that venepuncture did not influence the 5-H T levels

COMMENT

Carbachol and magnesium sulphate are both known to increase intestinal motility, and, in view of the increased intestinal sounds, they evidently did so in the present experiments Both drugs also raise the serum-5-H T significantly It is unlikely that they have another common site of action besides the intestine, and it is therefore reasonable to conclude that the 5-H T was liberated in association with increased intestinal activity

I am indebted to Prof M Weatherall for help and guidance in this work.

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6 Farrar, J T , Ingelfinger, F J *Gastroenterology*, 1955, 29, 789

New Inventions

DEVICE FOR REMOVING AN OPEN SAFETY-PIN FROM ŒSOPHAGUS OR BRONCHIAL TREE

AN open safety-pin, with point and head upwards, always presents a grave problem Attempts to remove the pin by direct traction lead almost invariably to puncture or tearing of the viscus, and fatal mediastinitis has often been recorded To try to reverse the pin so as to bring the loop-end upwards is equally dangerous The victims are usually young children, but the accident of swallowing an open safety-pin may happen in older people, and especially in the mentally afflicted.

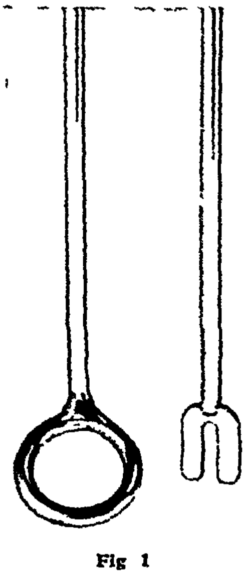

Fig 1

The three photographs are largely self-explanatory The ring and fork (fig 1), which I devised and first used some 10 years ago, have proved invaluable Until recently my instruments were home-made, but they have now been produced, in two sizes and slightly different shapes for adults and children, by the Genito-Urinary Manufacturing Co , 28a, Devonshire Street, London, W 1 The instrument for children is small enough to go through a child-size œsophagoscope or bronchoscope

The diagnosis is confirmed by plain X-ray examination. (The pin is found in the œsophagus far more commonly than in the trachea or bronchus) Under general anæsthesia, an appropriate œsophagoscope or bronchoscope is passed With the œsophagoscope a Barlow's high-power distally illuminated telescope is used to estimate the degree of œdema and the exact site of the loop of the pin. With the bronchoscope, which is distally illuminated, a direct-vision telescope is used. All mucus, food, &c , is aspirated, leaving the field of vision as clear as possible.

When the loop is clearly seen—and this is usually simple—the telescope is withdrawn, and the ring (which is fixed obliquely on the shaft) is passed beyond the pin-loop and brought up to engage it gently but firmly (fig 2) If there is any difficulty, the telescope is passed above the ring to give an excellent close-up view Once the ring is engaged, the fork is passed (again followed by the telescope if necessary) and applied directly on to the pin-loop Holding the ring firmly, pressure is applied to the fork, and the safety-pin is easily closed (fig 3) The ring, fork, and pin are then drawn into the endoscope, and all the instruments are withdrawn together

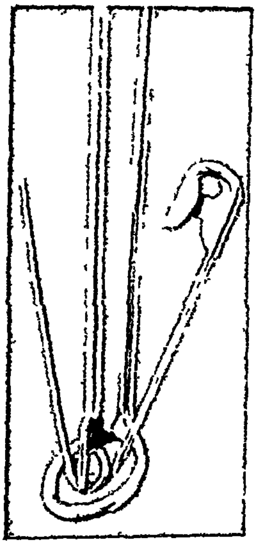

Fig 2.

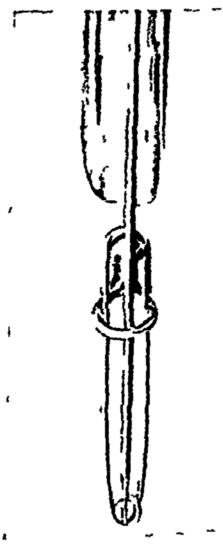

Fig 3

This procedure has never proved fatal nor has it caused serious after-effects

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DONALD BARLOW
M S Lond , F R C S
Surgeon

ŒSOPHAGEAL MICROPHONE

THE auscultation of heart and breath sounds during operation is very desirable, but it necessitates strapping a chest-piece on to the patient During cardiac and thoracic surgery, when it would be of most value, this is impossible

In 1954 Code Smith [1] of Toronto described a method of modifying the chest-piece of the conventional stethoscope by attaching a catheter with a rubber diaphragm, and passing it into the œsophagus, so allowing heart and breath sounds to be

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1 Smith C *Anesthesiology*, 1954, 15, 566

eard during operation. We have improved on this by attaching tiny microphone to the end of a catheter, which is then onnected to an amplifier, the 'Soniscope',[2] and so to a loud-peaker ('Cardiophone') The controls of the soniscope permit igh-pitched or low-pitched sounds to be excluded at will, and y sliding the catheter up or down the œsophagus, heart and reath sounds can be heard.

The catheter, with its terminal microphone, is best intro-uced into the œsophagus with the aid of a Macintosh laryngo-cope and a Magill's forceps when the patient is fully relaxed efore endotracheal intubation. It may also be used with an ropharyngeal airway and face mask. Heart sounds are best eard in the adult at 23–25 cm. from the incisor teeth.

The œsophageal microphone allows anæsthetist and surgeon ontinuous or intermittent monitoring of heart and breath ounds during operation. It is especially valuable for detecting arly evidence of cardiac irregularities or accumulation of ronchial secretions It is also useful in teaching

The 'Soniscope' and 'Cardiophone' are made by Faraday lectronics Ltd , 65, Fairview Road, London, S W 16

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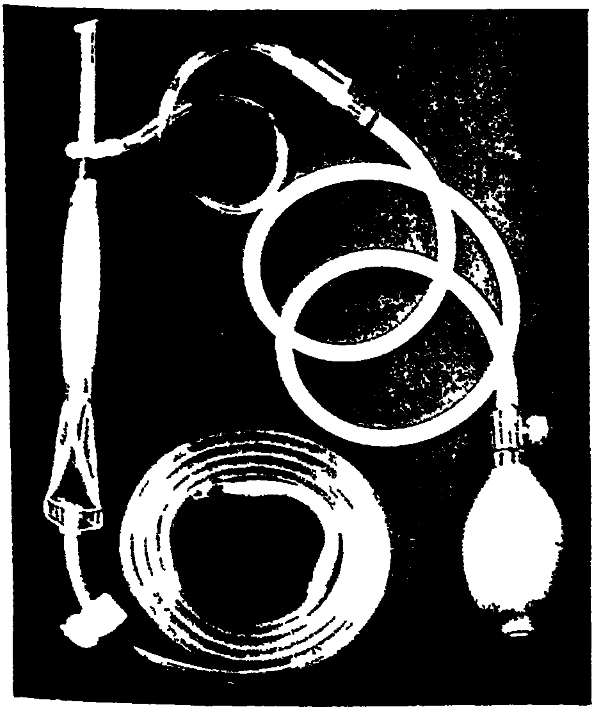
[2] Taylor, S , Fothergill, L *Lancet*, 1956, i, 1050

A SIMPLE PUMP FOR INTRAVENOUS INFUSION

PARTICULARLY since the introduction of disposable plastic infusion sets, neither the Higginson syringe nor the mechanical roller pump has proved consistently satisfactory The Higginson syringe has only one non-return valve, which tends to leak back, and the roller pump requires two hands for manipulation.

The new pump comprises a length of polyethylene tubing (bore IV/3) with a bulb and valve-control screw from a standard sphygmomanometer at one end. This unit contains both a simple non-return valve and a modified sleeve valve, which together completely prevent leakage At the other end of the tubing is a Luer adaptor which fits the air inlet of a disposable infusion set (see figure)



This apparatus is light and easy to control, and, because the valves prevent leak back, the pump tubing need not be clipped off. High pressure can be built up in the bottle, and when this is empty and the metal needle is exposed, the screw valve may be operated to release any residual pressure, thus avoiding the danger of air-embolism.

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JOHN GRACE
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Registrar

Medical Societies

MEDICAL OFFICERS OF SCHOOLS ASSOCIATION

BOXING was discussed by the Association at a meeting in London on Jan 7

Dr MACDONALD CRITCHLEY spoke of the injuries to the brain that result from head blows The commonest type of knock-out is now thought to be due to concussion of the medullary centres in the midbrain The extreme hypotonus, short duration of unconsciousness, and usually full recovery make it a unique response to injury Even if not very much harm is done in ninety-nine out of a hundred knock-outs the fact remains that a neurologist holds the central nervous system in some respect However doubtful the harm may be in some instances, it is beyond belief that such treatment is good for the brain There is no question whatever but that harm is likely to result from repeated injuries Speaking of serious damage to the second most delicate organ at risk—the eye—Dr Critchley mentioned Doggart's[1] work especially Although punch-drunkenness is practically limited to the professional boxer, it is a fact that the "groggy state" is seen in amateurs he referred to nine deaths in the amateur ring in this country since the end of the late war (there were two in December, 1959)

Dr J A WAYCOTT (Charterhouse School) admitted the undoubted benefits of boxing in developing muscular coordination and courage in adversity The sport is not as dangerous as some others But the "absolutely fundamental" difference, arising from the fact that the injuries in the ring are deliberate and intentional, distinguishes boxing from every other sport The chief target for such injuries is admittedly the brain No safeguards currently in use can possibly eliminate the fatal blow or detached retina Dr Waycott reminded his audience of the spectator's part The advocacy of cruel sports is a product not of reason but of the subconscious mind That is why it is so proof against arguments that appeal mainly to reason Natural displacements and sublimations are doubtless necessary, but it is vital to prohibit seriously objectionable outlets On balance the case against boxing, both medically and morally, is unassailable

Dr T A A HUNTER (Marlborough College) agreed that any sport whose primary purpose was the production of repeated head injuries must require very strong justification He wondered whether there was, in fact, evidence of such injuries resulting from schoolboy boxing

Dr D E DUNNILL (Bexhill-on-Sea) condemned professional boxing but thought that amateur boxing should be retained because it teaches a boy the ability to defend himself

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[1] Doggart, J H *A M A Arch Ophthal* 1955, 54, 161

Dr R E Smith (sometime medical officer, Rugby School) thought it quite wrong to compare amateur boxing with professional He stressed that many more injuries were sustained in other games and, anyway, what alternative was there if boxing were to go out?

Mr G A Hodges (director of physical education, Winchester College) said that after thirty years' experience he was convinced that boxing could be of great benefit educationally He condemned the bad features of much contemporary boxing and said that careful matching of contestants was essential This often involved leaving the best boxers out of a team in a match against another school and "unfortunately most schools won't accept this" He found that between 5 and 10% of boys wanted to box, and the feeble boy who suddenly found an unsuspected skill was often much helped in his outlook

Dr A W Henderson (St Edward's School, Oxford) thought that accidents occurred chiefly when amateur boxing was improperly supervised This, he felt, was an argument for more efficient supervision and control and not for the elimination of an admittedly dangerous sport

The Rev D L Graham (Headmaster of Dean Close School) mentioned his long experience of boxing, which included a period in charge of the sport at Eton He had been a boxer himself for more than forty years Although boxing undoubtedly gave a boy a certain status there were other and better ways of acquiring this Dean Close has abandoned boxing because of its objectionable features, and replaced it by judo

Several other speakers referred to judo as the obvious alternative If properly publicised and taught, it easily catches the schoolboy imagination It is superior to boxing as a means of self-defence, and the rules are framed so as to avoid injury Any hurt occurring during its practice is accidental and not deliberate, as in boxing Fencing and single-sticks were also mentioned as possible alternatives

The meeting concluded with unanimous assent to the suggestion that further evidence should be obtained on the hazards of amateur boxing Dr Critchley said he would report this to the president of the Royal College of Physicians

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Reviews of Books

Progress in Biochemistry Since 1949

Felix Haurowitz, distinguished service professor, Indiana University Basle S Karger London and New York Interscience Publishers *1959 Pp 357 60s*

In a preface Dr Haurowitz says that one of his reasons for writing this book was to keep abreast of the state of biochemistry, and this volume is in fact the fifth in his series of self-imposed refresher courses He has certainly done his prospective readers a service by giving them this survey of progress in his subject during the past decade As is inevitable in a book of such wide scope, the chapters are somewhat uneven, but the best are very good and the others worth reading The application of thermodynamic arguments to biochemical problems and the general aspects of biological oxidations are particularly clearly expounded, and, as might be expected from the author's special interests, the chapters on proteins and their derivatives (which take up about a quarter of the book) are very full and fair Dr Haurowitz himself adheres to the idea of a template for polypeptide synthesis which includes preformed protein as well as ribonucleic acid. Other chapters provide brief accounts of such varied topics as the biochemistry of lipids and carbohydrates (including amino-sugars and the several pathways of glucose catabolism), fat synthesis, hormones, antibiotics, and immunochemistry

The book can be highly recommended to those who have fallen behind in their biochemical reading, but it does assume a reasonable familiarity with the fundamentals of the subject References are plentiful and well chosen, and a glossary of over a hundred abbreviations affords both a sidelight on the popularity of such figures of speech among the professionals and enlightenment for amateurs not steeped in biochemical badinage

The Physiology and Treatment of Peptic Ulcer

Editor J Garrott Allen, M D Chicago University of Chicago Press London Cambridge University Press 1959 Pp 236 56s 6d

Here is an almost limitless subject, to judge from the volume of work, both observational and experimental, that has been pouring out over the years Nevertheless, and it is the achievement of the editor and his eleven noted contributors, condensation has been secured by intelligent sifting All the contributors have been under the influence of Dr Lester Dragstedt at some time in their career, and this monograph is their testimonial to him on his retirement The need to publish the work by the appointed day has imposed a praiseworthy economy, reflected in both conciseness and clarity, which will be fully appreciated by all readers There is an understandable bias towards physiology associated with the vagus nerve and vagotomy There is no cavil about the basic hypothesis on which experiment and argument are built, on the first page the dogma of pepsin is squarely stated by Dr Allen—the ulcer is a sequela of the digestive action of pepsin ergo, acidity is of paramount importance And so to a consideration of the phases of gastric secretion and their mechanisms, and the various experimental pouches used for their study A chapter is devoted to the cephalic phase, another to the antral phase, and it is followed by one on its clinical importance The details of radiological diagnostic technique and interpretation are well set out in a chapter by Dr P C Hodges, treatment follows Gastric ulcer is dealt with in the two final chapters, with an epilogue by the master himself on "what I would do if I had an ulcer" We hope that he has not, but we are grateful for his massive contribution to the subject during a very active professional life, and not least for this tribute, a succinct, informative, and readable monograph, which his work has evoked.

Clinical Chemical Pathology (2nd ed London Edward Arnold 1959 Pp 160 14s)—The new edition of this popular little book by Prof C H Gray illustrates the rapidity of change in this subject Test-meals are no longer considered in detail, but an account is now given of the van den Bergh reaction and its connection with non-conjugated and conjugated bilirubin, the value of the transaminase and other enzyme estimations in determining liver function, and diagnosis of cardiac infarction In the urine tests much, some may say too much, notice has been taken of the packaged tablet tests *Chromatography* has been introduced but very briefly The book continues to combine brevity with a remarkable completeness and clarity and will go on giving valuable service to one student generation after another

Complete Cookery Book for Diabetics (2nd ed. London H K Lewis For the British Diabetic Association. 1959 Pp 134 6s)—The second edition of this popular cookery book for diabetics by Iris Holland Rogers comes three years after the first It contains 33 new recipes, thus increasing further the great variety of meals offered in the exchange system More information is given about the use of sorbitol, and it is recommended that its caloric content should be assessed in diets for weight reduction. A useful new table of equivalent quantities of different sweetening agents is also included Another new section deals with the bottling of fruit, and additional valuable advice is given about invalid diets This book is a bargain at 6s, and should be welcomed by any diabetics who feel that the scope of their meals is restricted.

THE LANCET

LONDON 23 JANUARY 1960

Chemotherapy of Malignant Disease

THE effect of the nitrogen-mustard group of drugs in the control of leukæmia and reticuloses led to their use in the treatment of malignant conditions, and other substances were tried. Nitrogen mustard does destroy malignant tissue, but the dose that can be given is strictly limited by its toxic effect on blood-forming tissues—an effect which is made use of in the treatment of leukæmia. Nevertheless, ordinary therapeutic doses of intravenous nitrogen mustard have been used for the palliation of inoperable tumours, especially carcinoma of the bronchus, and it has caused shrinking of lesions with considerable, though temporary, symptomatic relief. WATSON and TURNER[1] used a combination of thiotepa (a mustard drug that can be given intramuscularly) and testosterone for the treatment of cancer of the breast, and they reported good results. A different drug is 5-fluorouracil,[2] an antimetabolite with an action similar to that of the drugs used in the control of acute leukæmias, and still another type, an antibiotic, actinomycin D, has been used in Hodgkin's disease.[3]

It was clear that better results might be obtained if the concentration of the drug actually reaching the tumour could be increased. A method of doing this was to isolate the circulation of the tumour area from the general circulation and then perfuse the isolated area with a really large dose of preferably a short-acting drug such as nitrogen mustard. We reviewed the preliminary results obtained with this technique some months ago.[4] CREECH and his colleagues now report further results[5] with what they describe as "regional" and "total-body" perfusion. In regional perfusion the artery and vein supplying the part are occluded proximally, cannulated in a distal direction, and connected to an extracorporeal circuit consisting of arterial and venous pumps and a bubble oxygenator. If the tumour area is in the limbs, tourniquets are used to isolate more effectively the perfused area. Perfusion of the lungs had been managed by using two extracorporeal circuits, one for the heart and lungs and one for the systemic circulation. In total-body perfusion, catheters are passed into the thoracic aorta and the inferior vena cava by way of the common femoral artery and vein. Before the perfusion is begun, as much marrow as possible is removed from the iliac crests and sternum, kept at 4°C, and returned to the patient by the intravenous route after the effect of the perfused nitrogen mustard or other drug has passed off. The chemotherapeutic agents used were nitrogen mustard, phenylalanine nitrogen mustard, and triethylenethiophosphoramide, a few patients were given 5-fluorouracil or actinomycin D. Recommended doses with nitrogen mustard vary from 0·6 mg. per kg. body-weight for upper-extremity perfusion to 1·0 mg. per kg. for pelvis perfusions.[6] KREMENTZ et al.[7] describe more fully the treatment these workers give for tumours of the extremities.

CREECH et al. now give results obtained with 145 patients treated by perfusion methods, these included 40 with malignant melanomas, 28 with sarcomas, 72 with carcinomas, and 5 with glial tumours. The proportion classed as "quiescent" after treatment was 46%, in 22% there was recurrence after initial response and in 25% there was no response, only 2 patients died from the direct effects of chemotherapy. Some interesting conclusions are drawn from their experience. Although regional perfusion methods produce concentrations of the chemotherapeutic agent 15–20 times as high as with systemic administration, none of the drugs tested "cured" the tumour. Nor is there evidence that any particular drug is more useful for the treatment of a particular tumour, sometimes an individual tumour will respond better to one drug than another, but this may not be true in the next patient with a similar tumour. CREECH et al. are trying to devise a "sensitivity test", but so far it is very crude. Depression of blood formation, especially leucopenia, is a complication that has often to be reckoned with when large doses of these toxic drugs are used. It is least troublesome in regional limb perfusions with good isolation when a short-acting drug such as nitrogen mustard is used, it is more serious when effective isolation is less feasible, as in pelvic perfusions, or when a longer-acting drug such as thiotepa is used, and it is most serious in total-body perfusions. In most of the 145 patients the depression was not serious, but in 19% of patients the white-cell count fell below 1000 per c.mm., fortunately, recovery from these severe changes can often be encouraged by transfusions of fresh blood and administration of steroids and antibiotics.

On the whole the best results have been obtained in the treatment of metastatic melanoma in the limbs, and better results have followed treatment of carcinoma of the genito-urinary tract, lung, and breast than elsewhere. "While in no instance has an advanced lesion in these areas been arrested, significant palliation has been afforded in some cases and in others a non-resectable lesion has been converted to a resectable one." Relief of pain has been observed in almost every case. These isolation-perfusion techniques can only be carried out in hospitals equipped to provide extracorporeal circulation. But the systemic use of these chemotherapeutic substances, even if less effective, can be carried out anywhere and some relief given to the patient. RAPHAEL and REILLY,[8] for example, gave standard nitrogen mustard to 56 patients with inoperable carcinoma of the bronchus and obtained significant palliation in 15

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[1] Watson, G W , Turner, R L *Brit med J* 1959, i, 1315
[2] Hall, B E , et al *Lancet*, Jan 9, 1960, p 115
[3] *ibid* 1959, ii, 900
[4] *ibid* 1958 ii 1321
[5] Creech, O J Jr , Krementz, E T , Ryan, R F , Reemtsma, K., Elliot, J L., Winblad, J N *J Amer med Ass* 1959, 171, 2069
[6] Creech, O J , Jr , Krementz, E T , Ryan, R F , Reemtsma, K , Winblad, J N *Ann Surg* 1959, 149 627
[7] Krementz, E T Creech, O J , Jr , Ryan, R F , Wickstrom, J *J Bone Jt Surg* 1959, 41A, 977
[8] Raphael, M , Reilly, C N *Dis Chest*, 1954, 25, 215

On p 206 of this issue, Mr Gordon Jack and his colleagues record results with the nitrogen-mustard drug tretamine (T E M , triethylenemelamine) in 43 patients with inoperable lung cancer 30 patients showed subjective improvement and in 10 " marked to complete " regression of the tumour ensued, the X-ray appearances returning to normal or near-normal in 4 of them They therefore recommend that tretamine, in a single dose of 20–30 mg (0 35 mg per kg) given intravenously, should be tried in patients with inoperable carcinoma of the lung There is now enough evidence for giving one of the nitrogen-mustard drugs to such patients, but not everyone will agree with the choice of tretamine Earlier indications [9] were that tretamine was one of the most toxic and one of the less reliable of the nitrogen-mustard drugs that had been given clinical trial [9], and Creech et al do not recommend its use Mr Jack and his colleagues had much trouble with hæmopoietic depression For the palliative treatment of malignant disease with nitrogen-mustard drugs, there still seems much to be said in favour of the less toxic members of the group, nitrogen mustard itself in the bis form (mustine) or the tris form (' Trillekamin '), or, if intravenous injections have to be avoided, the now well-tried thiotepa

Stereotaxic Operations on the Brain

Just over fifty years ago Horsley and Clarke[10] introduced the principle of locating points in the brain by reference to a three-dimensional frame applied to the head Originally the points of reference connecting the skull to the frame were the external meati and the infra-orbital margins, and these remain the basis of most alignments For many years work was confined to animals, but Spiegel et al [11] applied the method to the human brain and in the past decade an intensive attack has been made on the technical problems, which are considerable The original frames outlined the edges of a box, but a popular adaptation described by Leksell[12] used the principle of a movable arc with an electrode carrier that could slide along the arc, which represented part of the circumference of a circle An electrode or cannula of a length equal to the radius would terminate always at the centre of the circle, no matter where the point of entry was through the skull The instrumental accuracy can be brought to a high level The machine should be rigid but light, should have clearly defined points and lines for radiological identification, should be aligned with accuracy to the central ray of an X-ray tube, and should be reapplicable to the head in exactly the same position on separate occasions This is achieved most simply by leaving screws in the skull after the setting of all movable parts of the frame in relation to the screws has been recorded Unfortunately, accuracy does not depend solely on the design of the instrument Maps of different human brains have shown that the dimensions of internal structure vary independently of one another, much as do the features of the human face Even the most accurate averaged map cannot apply entirely to an individual brain, but the margin of error can be reduced by the use of proportions and of ventricular landmarks close to th target [13–16]

In treatment it is difficult to produce a large cerebral lesion that is accurate in size, shape, and centre Leucotomes,[17] diathermy, and direct current destruction have been used, and also the injection of sclerosing solutions [18] with or without prior separation of the local tissues Repeated small lesions require repeated insertions of an electrode, though a movable central stilette has been pushed in varying directions from the tip of a cannula in order to reduce the number of punctures through the rest of the brain

The purposes for which these methods have been employed have been restricted so far by the limitations of our knowledge of anatomy, physiology, and pathology Riechert [19] has summarised the indications, of which the commonest at present is parkinsonism Destructive lesions in the globus pallidus, ansa lenticularis, and nucleus ventralis lateralis thalami have produced better results in this disease than any other surgical procedure —a fact which has given great impetus to the development of stereotaxic methods The results have also been encouraging in hemiballismus, Huntington's chorea, athetosis, and other dystonias [20–23] Pain relief is particularly difficult to assess Attempts have been made to destroy the nucleus ventralis posterior and the nucleus centrum medianum thalami, apparently with some success [24] The intractable " thalamic " pain associated with vascular lesions is said to be relieved by destruction of nucleus centrum medianum, which may receive fine fibres running through the reticular formation, probably by multisynaptic paths [25] Epilepsy due to bilateral or central foci can be tackled most suitably by stereotaxic methods aimed at deep structures—either nuclei or tracts—to break pathways concerned in the spread of seizures targets have included the internal medullary lamina of the thalamus,[26] the fornix,[27] and the temporal isthmus [28] The pituitary gland can be entered by such means, but in view of the proximity of the optic nerves and chiasma, open operation will probably remain preferable in most cases In the treatment of schizophrenia the results of destruction of the nucleus dorsalis medialis are roughly comparable with those of the " standard " prefrontal leucotomy

Every new piece of information about the results of stimulation and of temporary or permanent paralysis of

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9 See Lancet, 1954 i 1118
10 Horsley V Clarke, R H *Brain*, 1908, 31, 45
11 Spiegel, E A Wycis H T , Marks M , Lee J *Science*, 1947, 106, 2754
12 Leksell, L *Acta chir scand* 1949, 99, 229

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23 Martin, J P , McCaul, I R *Brain*, 1959 82, 104
24 Talairach, J , de Ajuriaguerra, J , David M *Pr méd* 1950 58 697
25 Bowsher, D *Brain*, 1957, 80 620
26 Spiegel E A , Wycis, H T *Acta Neurochir* 1952 2, no 3 4
27 Hassler, R., Riechert, T *ibid* 1957, suppl 5, p 330
28 Turner, L A *Int Congr Neurosurg* 1957 abstract p 105

each known structure in the brain will enhance the accuracy of stereotaxic methods The dynamic view of brain function lays greater emphasis than ever on tracts of internal communication We hope that by means of research advantage will be taken of the technical methods now within our reach

Bone-marrow Preservation

BONE-MARROW " grafts " or transfusions are being increasingly used [1] Such grafts consist of marrow cells obtained by aspiration from the sternum or the iliac bones They have so far been used in three conditions in aplastic anæmia of unknown origin, or known to be due to accidental exposure to radiation, in acute leukæmia following whole-body irradiation designed to destroy the abnormal marrow and to suppress immune reactions, and after treatment of widespread malignant disease by large doses of nitrogen-mustard drugs The possible sources of bone-marrow and the various methods of using it have been reviewed by WILSON [2]

Bone-marrow can be autologous (from the same patient) isologous (from an identical twin), or homologous (from another person, usually selected because his blood-groups are as similar as possible to those of the recipient) Autologous marrow is used in two ways In the treatment of malignant disease by nitrogen mustard, marrow can be withdrawn, kept at 4°C for one or two hours, and then reinfused, since the action of the mustard drug is over in about an hour, with this method no elaborate storage techniques are required The other use of autologous marrow is to draw off healthy marrow from a patient with leukæmia at a time when he is in remission, spontaneous or induced by drugs, this marrow is stored until a relapse occurs, and the patient is treated by total-body irradiation of 570–600 r followed by intravenous infusion of this stored normal marrow This method has been applied by McGOVERN et al [3] in three cases of acute lymphoblastic leukæmia, one patient died nine days after irradiation with the leukæmia still present, one died after twenty-three days and no postmortem evidence of either leukæmia or repopulation of the marrow was found, in the third case the marrow reverted to normal within seventeen days and there was complete hæmatological and clinical remission

Homologous marrow can also be used with or without storage, though storage is now more usual Much more marrow is required than for diagnostic taps, and WILSON considers that the sternum and the posterior ilium are the sites most likely to give a satisfactory amount of cells BIERMAN and KELLY [4] found that a single puncture of the posterior ilium yielded 10–20 ml of material with minimal admixture of blood WILSON prefers multiple aspirations with the donor under general anæsthesia, using both sternum and posterior ilium he obtained yields of from 3×10^{9} to 16×10^{9} cells The cells obtained by these aspirations are usually received into one of the balanced salt solutions, such as Hank's solution,[5] to which an anticoagulant has been added If the marrow is to be administered without storage, sequestrene (ethylene di-amino-tetra-acetate) 1–2 mg per 20 ml of solution is added, but if the marrow is to be frozen for storage, heparin (which must be free from phenol) 10 mg per 100 ml is preferable

For storage, all workers recommend freezing in the presence of glycerin and keeping at −79°C, with reconstitution just before the marrow is to be used Storage at −20°C does not seem to be satisfactory, MOLLISON et al [6] found that when red blood-cells were stored at this temperature a large proportion were lost by hæmolysis during the recovery process, and the same may apply to marrow cells Cooling to −79°C (the temperature of a mixture of solid carbon dioxide and industrial spirit) a suspension of cells in a glycerin solution dates from the demonstration by POLGE et al [7] ten years ago that fowl semen could be preserved by this method and the application by AUDREY SMITH [8] of this technique to the preservation of red blood-cells

NEWTON et al [9] at the Westminster Hospital suspend the marrow in a mixture of Hank's solution, inactivated human AB serum, 'Bacto' yeast extract, glucose, penicillin, streptomycin, and heparin, then they free the mixture from unwanted tissue particles by passing it through suitable stainless-steel filters of various grades The filtered suspension is mixed with glycerin to give a final glycerin concentration of 15% v/v After equilibration for ten minutes, 7 ml portions of the mixture are sealed into glass ampoules "and cooled at 1°C per minute to −15°C and thereafter at a rate not exceeding 10°C per minute to −79°C" The necessity for differential cooling, with a relatively slow rate down to −15°C and then a much accelerated rate below −15°C, is a serious technical snag, and special apparatus has been designed to overcome it PEGG and TROTMAN,[10] of the Westminster team, have designed an electrical apparatus that will take nineteen of the 7 ml ampoules at one time and cool them in the desired manner, others have used commercially assembled apparatus The frozen marrow is reconstituted by rapid thawing in a water-bath at 38°C, and then a half-volume of 35% glucose in balanced saline solution is added and well mixed, two minutes later an equal volume of balanced saline is added, followed by a further volume of saline in another two minutes This produces a cell-suspension in 2 5% glycerin and slightly hypertonic glucose-saline solution, and such a mixture can safely be given intravenously In the U S A somewhat more elaborate techniques making use of multiple plastic packs have been described [11] These disposable plastic packs are convenient and they ensure sterility, they are in common use for blood-transfusion work in the U S A, but in this country they are expensive

Marrow from living adult donors has been most used, but this is clearly no light undertaking if a general anæsthetic has to be given to enable enough marrow to be obtained without much pain and discomfort, marrow donation is much more incommoding than blood donation Other sources have been explored FERREBEE confused with established fact It is by combination of fact and speculation that much scientific progress has been achieved Tanner and his colleagues have provided themselves and other workers with a target for tomorrow

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CHOLINESTERASE ACTIVITY IN THE CEREBROSPINAL FLUID

THE basal ganglia have a considerably higher content of acetylcholine-splitting enzymes than the rest of the central nervous system [1] Very active acetylcholine synthesis has also been demonstrated in the caudate nucleus of dogs,[2] indicating a lively local metabolism of this substance Here, as elsewhere in the cerebral grey matter, the enzyme is predominantly of the "true" ("specific" or aceto-cholinesterase) variety,[3] probably identical with that found in erythrocytes

Unilateral intra-carotid injection of an anticholinesterase drug, diisopropylfluorophosphate (D F P), produces in rabbits an involuntary circling behaviour [4], the associated assymmetrical inhibition of cholinesterase in the brain is most severe in the caudate nucleus and the frontal cortex [5] Administration of D F P to subjects with schizophrenia was followed in some cases by "activation" of the psychosis, or the reappearance in chronic cases of the florid symptoms which had characterised the onset of the illness, these patients showed fewer electroencephalographic changes, and had less severe gastrointestinal and cardiovascular symptoms, than manic-depressive or healthy people who received the same drug [6]

The cholinesterase activity of the cerebrospinal fluid is very low, and its physiological significance uncertain, but the assumption that its lèvel reflects the enzymatic activity of the brain has led to investigations in neurological and mental disorders High true-cholinesterase activity was found in the cerebrospinal fluid in tumours of the central nervous system and in tuberculous meningitis, low values in poliomyelitis, general paresis, and epilepsy [3] Jefferson [7] found normal cholinesterase activity in the cerebrospinal fluid of fourteen patients with disseminated sclerosis, and he concluded that long-continued depression of pseudo-cholinesterase ("non-specific" or butyrocholinesterase) is unlikely to play a major part in the pathogenesis of this condition This conclusion followed the observation that anticholinesterase agents can provoke demyelination in man [8] Bernsohn et al [9] have reported high true-cholinesterase activity in myasthenia gravis, in the Guillain-Barré syndrome there was a considerable increase of ali-esterase activity, probably secondary to the high albumin content of the cerebrospinal fluid

In a group of patients with schizophrenia (in most cases chronic) Hungarian workers[10] have found much-reduced true-cholinesterase activity in the cerebrospinal fluid, the values increasing in parallel with clinical improvement after electroconvulsive treatment Other, presumably also long-stay, patients with general paresis, epilepsy, or mental defect showed only moderate inhibition of cholinesterase activity in their cerebrospinal fluid, while three acute cases (two of neurasthenia and one of paranoid state) had normal values. The estimations were carried out by a titrimetric method—not with the customary, and more reliable, manometric method—and the nutritional state of these patients is not described. These findings are at variance with those of Mutrux and Glasson,[11] who reported that true cholinesterase, pseudo-cholinesterase, and ali-esterase were present in various amounts and combinations in the cerebrospinal fluid of a hundred psychiatric patients but could find no pattern characteristic of diagnostic groups, including schizophrenia

THE DISTURBED CHILD GROWS UP

THOUGH child-guidance clinics are increasing, their number is still insufficient, and many are understaffed. Somewhere between 5 and 12% of the school population require referral to a clinic,[12] and Dr Mildred Creak [13] has suggested that the clinics, overworked and with staff often inexperienced and in academic isolation, may fail to meet this challenge

Disturbance in the individual child can now be more clearly delineated [14], but diagnostic groupings are still unestablished, and accordingly some psychiatrists have wished to abandon diagnosis altogether—a proposal which Kanner [15] has rightly criticised as retrograde It is clearly important to find out what happens to these children when they grow up, and the studies of O'Neal and Robins,[16–18] though still incomplete, help to fill this gap in our knowledge

Their follow-up of some 500 children seen at a psychiatric clinic in St Louis thirty years ago, compared with a matched control group, showed an increased incidence of adult psychiatric disorders, the excess being largely accounted for by schizophrenia and sociopathic personality Neurotic illnesses differed little between the two groups Adults diagnosed as having sociopathic personalities had mostly been delinquents in childhood, while many of those who became schizophrenic had presented problems of aggressive antisocial behaviour Those patients who were psychiatrically well as adults came chiefly from the group of children with neurotic problems Of the delinquent children, 38% had not been arrested as adults, but the rate, severity, and chronicity of adult crime in the delinquent group was nevertheless high The incidence of violent deaths among the males was striking 4% had been killed, and no less than half of these had been shot by the police Comparing a group of aggressive antisocial children who became schizophrenic with a similar group of children who in adult life were without psychiatric disease, O'Neal and Robins found that the preschizophrenics had had more symptoms of all kinds, and that more areas of function had been disturbed

Antisocial behaviour in the preschizophrenic child has been previously reported by Morris et al [19] Clearly there may be considerable differences between the clientele of an American child-guidance clinic thirty years ago and a British clinic today, but the evidence so far suggests that it is the antisocial child rather than the neurotic who is most in need of help

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Special Articles

RADIATION EXPOSURE: CREDIT AND DEBIT *

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MEDICAL RESEARCH COUNCIL'S RADIOBIOLOGICAL RESEARCH UNIT, HARWELL, BERKSHIRE

THE original aim of radiation protection measures was the prevention of radiation-induced somatic damage in radiological workers, it was supposed that damage was induced only if the exposure exceeded some threshold, and the functions of the protection authority were to assess the scientific evidence on the position of this threshold and ensure that it was not crossed Today a quite different problem has to be faced, since we now believe that there is no dose threshold for the induction of genetic damage, and that there may be no threshold for the induction of some types of somatic damage

This new concept of the nature of radiation hazards calls for a new approach to the problems of protection The only ethically admissible approach appears to be to assess, as accurately as present knowledge permits, the good and the harm that would be done by each exposure to ionising radiation, and on this assessment to base the decision whether to make the exposure or not The credit side of this balance sheet should be drawn up by those advocating the exposure, the debit side by the protection authority, the decision whether or not to proceed with the proposal, which is a matter not of science but of national policy, should not necessarily be taken by scientists alone This procedure is clearly an ideal to be aimed at, and it would be difficult to apply it in all cases today One of its difficulties lies in that fact that the benefits obtained from most uses of ionising radiation, especially its medical applications, are immediate and their causal connexion with the exposure is obvious, whereas the damage, especially the genetic damage, may not become apparent for many years and its connexion with the exposure is usually undemonstrable, in other words, the damage constitutes a long-term debt to be paid eventually by somebody other than the borrower Another and more immediate difficulty is that of estimating the magnitude of the somatic and genetic debts

Some attempts have in fact been made to draw up balance sheets for particular uses of ionising radiation One example is to be found in the interim report of the Committee on Radiological Hazards to Patients,[1] which dealt with mass-miniature radiography of the chest Referring to the year 1957, the committee reported

Credit	
Cases found	
Pulmonary tuberculosis	17,835
Cardiac abnormalities	12,000
Pneumoconiosis	9400
Lung cancer	2362
Debit	
Cases possibly induced but yet to appear	
Leukæmia	20 (maximum)

The debit side of this balance sheet is incomplete, in that only one component of the somatic debt was estimated, and the genetic debt is not mentioned How can it be calculated?

To estimate the total genetic debt arising from a given exposure it is necessary to know, for every deleterious condition, (*a*) the genetic mechanisms by which it is maintained in the population, and in particular how its incidence is related to the mutation-rate of genes concerned, and (*b*) how the mutation-rate is related to radiation exposure The genetic mechanisms by which many conditions are maintained are unknown, they include numerically important conditions such as hæmolytic disease of the newborn, diabetes mellitus, manic depressive psychoses, schizophrenia, exophthalmic goitre, pernicious anæmia, fibrocystic disease of the pancreas, most deaf-mutism, and the majority of congenital anomalies[2] For these it is therefore impossible at present to assess the genetic debt created by any given exposure This may be less important than it appears at first sight, because there is reason to suspect that some of them, at least, may be maintained by causes other than mutation pressure, and their incidence may therefore be affected little, if at all, by changes in the mutation-rate, where this applies the genetic debt created by radiation would be small, even though the condition itself is relatively common

On the other hand, there are many conditions which there is good reason to believe are the expressions of single mutant genes maintained in the population by mutation pressure, their incidence in a population in genetic equilibrium will be directly proportional to the mutation-rate, and in respect of them any radiation exposure will create a genetic debt The incidence of defects of this type in the population of Northern Ireland has been reported by Stevenson[2] He listed 142 such conditions, and reported their incidence at birth and in the surviving population Many had relatively unimportant effects on the individual—e g , alopecia areata, spasm of the eyelid, camptodactyly, polydactyly, Garber's toe anomaly, such minor defects totalled 23,132 per million births and had a similar incidence in the surviving population Many others, however, had relatively serious effects on the individual they included achondroplasia, ectrodactyly, aniridia, congenital cataracts, infantile glaucoma, retinoblastoma, some deaf-mutism, megacolon, amaurotic idiocy, ichthyosis congenita, hæmophilia, and sex-linked muscular dystrophy, such major defects totalled 11 727 per million births, with a smaller incidence in the surviving population These incidences may be taken as representative of the British population

The relationship between the human mutation-rate and radiation exposure is much less certainly known, it is usually expressed in terms of the mutation-rate-doubling dose—i e , the genetically effective radiation dose that would induce as much mutation per generation as arises spontaneously The United Nations Scientific Committee[3] concluded that the doubling dose for man probably lies somewhere in the range between 10 and 100 rem For acute exposure of spermatogonia in adult male mice the doubling dose is about 30 rem[4] and for chronic exposure about 95 rem[5] In what follows it will be assumed that the doubling dose for man is 100 rem, and it seems probable that any error introduced thereby will be in the direction of optimism

We can now estimate the component of the genetic debt due to single mutation-maintained genes incurred the year Admissions of elderly patients rose in 1958 when the unit began taking them in for short periods, to relieve relatives for holidays and so on It thus includes a number who are normally day patients

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* Based on a paper presented, by invitation, to the International Commission on Radiological Protection, July 24, 1959

[1] Interim Report of the Committee on Radiological Hazards to Patients London, 1959

[2] Stevenson A C. *Radiation Research*, 1959, suppl. 1, 306

[3] Report of the United Nations Scientific Committee on the Effects of Atomic Radiation New York 1958

[4] Russell, W L., Kelly, E M *Science*, 1958 127 1062

[5] Carter, T C., Lyon, M. F , Phillips, R. J S *Nature, Lond* 1958, 182, 409

Social Clubs

The unit has an active social life and much contact with the life of the town

Twice weekly, social evenings are held, attended by many people from outside One is a Darby and Joan Club, run by the W V S , the other is open to all patients (including day patients and outpatients), ex-patients, relatives, friends, and staff. Attendance at the latter averages 150, including some who have been coming regularly for nine years Meetings of Alcoholics Anonymous are sometimes held with the club Some of the mental-health officers attend, but otherwise the club is entirely a hospital service

Day Patients

Day care in the Oldham service is directed primarily to the needs of elderly patients Of 193 day patients, 103 were over sixty years, most of them with a diagnosis of senile dementia This contrasts with some other day units, in which depressive illnesses predominate and few senile cases are treated (Harris 1957, Smith and Cross 1957, Freeman 1959) Even the nearby service at Bolton treats few senile day patients

One reason for the preponderance of elderly patients is probably the admission policy Where a day unit is geared to the treatment of neurotic and affective disorders, senile patients will be unwelcome, because of their chronicity and because they will tend to influence the therapeutic atmosphere unfavourably (Craft 1957) Conversely, a unit where there is a high proportion of senile patients is less likely to be regarded as suitable for young neurotics, who may well find it depressing Again, the population of Oldham gives an impression of stolidness and mutual support which suggests that severe neurotic disorders may be less prevalent than in some other districts Whether the existence of a different kind of day hospital would attract previously undisclosed cases is a matter for speculation Blacker (1946) has pointed out that the attitude of general practitioners to units of various types can affect the apparent incidence of different kinds of cases

Day care arrangements at Oldham are flexible, so as to allow for the needs of relatives Some patients attend seven days weekly Transport of these patients is a considerable burden on the local authority, but their journeys are confined as far as possible to " off peak " hours Until recently, there was no separate accommodation for day patients, but a garden pavilion has now been converted to take about 30 female psycho-geriatric patients, and similar facilities are to be provided for the men

Outpatients

15 sessions are held weekly, though the medical staff is so small 2 of these are taken by a clinical assistant, who forms a link with the local industrial rehabilitation unit, of which he is the medical officer Evening and Saturday sessions allow patients to attend early in the illness, without loss of work Two ECT sessions are held weekly and psychotherapy is given as far as possible

Both nurses and mental-health officers spend a period at the outpatient department, attending interviews and helping with case-histories A similar arrangement in East Anglia has given excellent results (Pargiter and Hodgson 1959) The social work of the mental-health officers is valuable if patients do not keep their follow-up appointments

The average annual total of outpatient attendances is now about 5000 After reaching a peak of 415 in 1956, the number of new cases fell to 386 in 1957 and 314 in 1958 This may perhaps be interpreted as the effect of an established service, once it has overcome the backlog of cases for which facilities were not previously available The peak of new cases in 1956 is almost exactly the same as the number treated by the Bolton service in 1957 from a population of almost identical size (Leyberg 1959)

Domiciliary Visits

These are made by the consultant, usually accompanied by a mental-health officer The actual number is about 350 yearly, but most are informal Many are to elderly patients on day care who have missed attendance A visit will often reveal difficulties in the home Timely help may obviate admission or confinement to the house Each mental-health officer makes about 1000 home visits yearly, and they are the most important part of his work Because of this, visits by nurses on the Worthing pattern (Carse 1959) are not needed

Discussion

In altering treatment policy, one must ensure that the change is not spurious, merely shifting responsibility from one authority to another At Oldham there has been no increase in local beds, except for the psycho-geriatric unit for 32 cases Yet whereas practically all patients needing treatment used to be transferred to the neighbouring large mental hospital, this number is now a mere trickle Very few patients have been transferred to mental-deficiency hospitals and part-III accommodation

The number of psychiatric beds in use, at 1 per 1000 of the local population, is about a third of the national average This suggests that an extension of community care, using peripheral psychiatric units, with an emphasis on outpatient clinics, domiciliary visiting, day treatment, and local-authority services, could considerably reduce the work of the large mental hospitals It is possible that this might save money, but by no means certain, for adequate community services are likely to be expensive in manpower, buildings, and transport (Colwell and Post 1959)

The main advantage to be looked for, however, is an ending of the segregation of the mentally ill into units which are often remote from their homes This not only causes distress to them and their relatives (who may have great trouble and expense to visit them) but makes it harder for them to return to normal life

Clearly, there is room for much variation in response to local needs A community service can be established in a compact urban area like Oldham much more easily than in a thinly populated district Specialised facilities cannot be available in all peripheral units Also, a unit with a small number of beds is in danger of being clogged with chronic cases However, with more geriatric units and better supportive services in the community, admission might be more selective or for shorter periods

Community services of varying patterns have already come into being in several parts of the country The Worthing service (Carse et al 1958) is provided entirely by the hospital and has no formal links with the local authority In York there is an integrated service, with a psychiatrist appointed jointly by hospital and local authority, but as yet no day-care facilities Nottingham (Macmillan 1958) has been a pioneer in community care, with psychiatric services based on the local mental hospital—which is much less remote than most The Nottingham service offers repeated short-term admissions for chronic cases, which are not excluded from the benefits of community care But the most suitable unit for the rehabilitation of chronic patients remains a matter of controversy (Baker 1958)

To this evolving picture of community mental care, the experience of the Oldham service can make an important contribution

My thanks are due to Dr Arthur Pool, consultant psychiatrist to the Oldham and district hospital group, and Dr J T Chalmers Keddie, M O H for Oldham, and their staffs I am also grateful for information and advice from Miss E M Brook of the General Register Office, Dr J S B Mackay of the Manchester Regional Hospital Board, Mr W A J Farndale of the Bethlem Royal and Maudsley Hospitals, Dr J H Kahn, and Dr Doris Odlum

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DRUG ADDICTION

THE Interdepartmental Committee on Drug Addiction, whose chairman is Sir Russell Brain, has issued an interim report[1] on two topics (1) drugs, such as carbromal and bromvaletone, which have an effect on the central nervous system but which are not appropriate for control under the Dangerous Drugs Act, and (2) the incidence and consequence of anæsthetists becoming addicted to the gases and vapours they employ

Carbromal and Bromvaletone

These drugs, the report remarks, are merely two examples among various drugs at present on sale to the public without restraint, the injudicious use of which may nevertheless be attended by dangers both to the individual and to the community But their properties are such that they do not qualify for control under the Dangerous Drugs Act, 1951, or the Therapeutic Substances Act, 1956, and the Poisons Board have so far felt unable to recommend them as poisons for control under the Pharmacy and Poisons Act, 1933 The committee accordingly recommended that in general any drug or pharmaceutical preparation which has an action on the central nervous system and is liable to produce physical or psychological deterioration should be confined to supply on prescription. An independent expert body should be responsible for advising which substances should be so controlled.

Addiction to Anæsthetic Gases

The committee agree that, with the apparatus at present in use, the preliminary sniffing of the gases immediately before administering them to a patient is a recognised and indispensable precaution. And to the great majority of anæsthetists such a practice offers no encouragement to addiction. " So far as we can discover less than twenty cases have come to notice over the past eleven years " but in two known instances throughout the country in eleven years patients' lives have been endangered " " We are convinced ", the report continues, " that anyone who is addicted to the inhaling of anæsthetic gases or vapours should not be entrusted with their administration the responsibility for dealing with this irregularity rests in the first instance with the anæsthetist's professional colleagues any arrangements made should provide for immediate action by the surgeon if an anæsthetist appears to be incapable of carrying out his duties "

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[1] Drug Addiction Interim Report of Interdepartmental Committee H.M Stationery Office Pp 8 6*d*

In England Now

A Running Commentary by Peripatetic Correspondents

YESTERDAY morning at the tea-break conversation turned to the Christmas concert The plaster-room sister deplored the present basis on which consultant appointments were made It was well known, she said, that such qualities as hard work, ability, integrity, humanity, and charm were no longer considered important, but why couldn't appointments committees at least consider the candidate's suitability as material for the Christmas concert? In a passive not active role, she hastened to explain Names that rhyme easily, personal eccentricities large feet, ears, or nose, a beard, a lisp, a drawl, a stutter, dropping the final " g ", a bow-tie, a loud waistcoat, gesticulating with hands or shoulders, turning X-rays upside down, twisting the legs round each other, wearing the white coat off one shoulder like a sari, all these, for instance, were clearly desirable qualities

The idea appealed to me After all we are a rather dreary lot—hard-working, well-intentioned, but colourless and uninspiring Since 1948 every selection committee on which I have sat have spent their time trying to judge between identical candidates all trying very hard to conform in every respect to the ideal mean I thought of the gay and colourful students who became prematurely middle-aged in the quest for promotion, could this early inhibition be the reason for their argumentativeness when they finally reached their goal? I thought of my own seniors between the wars—swashbuckling personalities, physicians who took a pinch of snuff at every bed, surgeons who smoked cigars in outpatients and theatre Yes, the plaster-room sister was right, we are grey and colourless I apologised to her, regretted that I could not afford to resign, but hoped that my successor would provide better material With a ghost of a smile she said that she hadn't meant that at all, indeed she hoped I would not resign—at least not just now This half compliment was unlike her, so I thanked her and we returned to the outpatients

My children laughed uproariously at the concert I seemed to miss the point of many jokes which amused the nurses and residents I recognised the parodies of some of my colleagues but was bewildered by a ludicrous figure whose eccentricities were loudly appreciated by everyone else

Only the next day did it dawn on me that perhaps the plaster-room sister had not been suggesting a new principle so much as the restoration of an old one Before 1948 perhaps selection boards gave bonus points for eccentricities and this admirable habit has merely been in abeyance All she had proposed was its restoration

* * *

When I arrived I was met in the mortuary by the senior resident, but it soon transpired that vital clinical information was in the hands of a junior house-officer who had not yet come. I made a noise indicative of displeasure and impatience " Shall I bleep her for you? " asked the resident Visions began to form in my mind of some quaint punitive ceremony, carried out late at night in the residents' quarters, using a rubber truncheon or perhaps one of those painful-looking medieval spiked balls attached to a length of chain Fortunately the house-officer arrived before I had time to pronounce sentence

Later, while I was browsing over a rather odd piece of lung, and the residents, satiated with morbid anatomy for the time being, were gossiping in a corner, the air was suddenly filled with an eldritch, insistent piping, and they scattered like guilty schoolboys Seeing my astonishment, the senior resident gently initiated me into the mysteries of the hospital's new call-system

We really must have one in our laboratory Then, when I am discussing a missing specimen with a querulous surgeon, I shall no longer need to go to the door and shout " George! " With smug suavity I shall reach for the telephone " Mrs Ogmore, bleep the chief technician for me, will you? "

* * *

The telephone is generally felt by our profession to be among the major plagues of modern life but its absence a hundred years ago certainly wasted a vast amount of doctors' time and patients' guineas I have been reading the private diaries of a consulting physician in the 1860s who lived in Marylebone and had a high-class practice, including Royalty He would be called, let us say, to Frogmore, by telegram—without any indication of the degree of urgency or any possibility of further inquiries Dropping everything, he would go by brougham to Paddington, take a train to Windsor and then—a cab being unobtainable at the station as often as not—walk across the Park There are hardly any records of his being met by a conveyance At Frogmore he finds a baby with green stools, prescribes for it, and returns to London by the same laborious methods Next day he cannot ring up to inquire but must repeat the performance only to find the baby quite recovered and normal When this has happened several times, a hint is dropped by an equerry that he is visiting too often Even in London there are frequent notes "Visited but found no one at home", a situation which a telephone call would nowadays have obviated

The other modern—or relatively modern—devices which strike one by their absence are thermometers and baby scales None of the four Royal babies seem ever to have been weighed The first was "small" The second is "larger and heavier than his brother", and so on The small clinical thermometer was only invented by Clifford Allbutt in 1866 and its more monstrous predecessors would doubtless have frightened out of her wits a Princess who expressed—through a lady-in-waiting—"a little alarm" at the doctors taking out their watches to count her pulse Quinine was the master drug of the period, exhibited for practically everything from orbital neuralgia to "a strengthening medicine" after sea-sickness Except for a variety of preparations of opium, few of the drugs used, other than aperients, would appear to have any potency according to modern ideas and the solemn consultations which, in face of serious illness, resulted in changing from one elegant mixture to another equally elegant and equally harmless fill one with pity tinged with superiority And in 1864 the problems of a royal confinement were complicated by the claims of a lady styled "Purveyor of Wet-Nurses to the Royal Family"

* * *

Anxious Patient Oh, Doctor, what is the result of the Test?
Sporting Doctor Ah yes, there's another day to go yet, but Peter May and Barrington are
Anxious Patient I mean did you find any cysts in my stool?

* * *

My nose is pressed down on the grind-stone
My schedule is loaded with stress
My diary teems with appointments
My desk's in a terrible mess
Without any hope of assistance
I ask how much more I can do
I envy the lowly amœba—
Designed to divide into two

When conflict remorselessly rises
Within its primordial soul,
It solves its emotional crisis
By splitting its cellular whole
No ruthless attempt at suppression
Produces guilt feelings inside
It promptly resolves on secession
And gently begins to divide

Its slow pseudopodial motion
Has none of the joy of a walk
Its life must be drab in its ocean—
All wet and unable to talk.
Unicellular social position
Is very precarious, it seems,
But the function of binary fission
Belongs to the cosmos of dreams

Letters to the Editor

THE COST OF DRUG TREATMENT

SIR,—May I add a few thoughts to the excellent articl by Dr Miller and Dr Smith (Jan 2)? These have come into my mind during recurrent attendances at economy committees

Waste is inevitable and had better be accepted Some is justified because the doctor feels that it is better to give the drug and be on the safe side This is no greater waste than the time laudably spent listening to irrelevant histories, percussing resonant chests, and answering night calls that are not urgent A great deal could, of course, be avoided if we were not so stupid and ignorant. But we are as we are made, and if the public wants to attract a better type into the profession they will have to pay them more than we waste on drugs Waste on drugs is preventable in the sense that road accidents are preventable—that is to say, they cannot be stopped

The patients' demand for drugs will increase This was high enough when the bottle of medicine was pharmacologically inactive But as more drugs are known to be effective, fewer patients will be willing to see themselves as the few singled out for whom there is no remedy As the public becomes more sophisticated, so also will the drugs that are needed to satisfy them This is regrettable, but no more so than many other things we have to put up with

The drug bill should be a source of national pride, not shame The public takes the view from time to time that vast sums of its own money should be spent on projects that seem right These activities are not necessarily useful They are regarded more as solemn obligations or demonstrations of status, or even as acts of glory I refer, for example, to pyramids, crusades, cathedrals, governing other people, railways, sports stadia, space, medicine, air lines, or television Now there is no reason why the drug bill should not be put on the list It would mean a change of attitude, but nothing beyond our competence Medicine is already on the list, and so is the production of new drugs, provided it is done only by foreigners We could then regard its steady annual growth with quiet pride, instead of with shame and mutual recrimination

But it may be objected that without restriction the bill would reach intolerable proportions I doubt whether that would happen It seems to be controlled by its own laws of growth, and no doubt would be as unaffected by future praise as it has been by present condemnation

London, W 1 J B HARMAN

SIR,—In their very interesting article Dr Miller and Dr Smith included a reference to the weekly cost of the three main anti-tuberculosis drugs given at home The figures given for streptomycin of 14*s* 5*d* weekly and for isoniazid 1*s* 10*d* weekly are approximately of the order of magnitude I would expect I am, however, extremely surprised at the figure of £1 2*s* 11*d* weekly for treatment with *p*-aminosalicylic acid (P A S)

Based on hospital costs, I had always reckoned that treatment with P.A S cost between 3*s* 6*d* and 7*s* (or a little more) weekly, depending on the particular preparation used, and certainly I would expect the cost of P.A.S to lie between that of isoniazid and streptomycin.

I have discussed the figures with our hospital pharmacist and with a local retail chemist, and I have been unable on the ost generous estimates of costing to obtain a weekly figure for A.S (20 g daily) much in excess of the cost for streptomycin.

Considering the very substantial amount of anti-tuberculosis reatment at present carried out at home, I feel that the figure or this treatment is of some importance, and I would be most nterested to know how the figure of £1 2*s* 11*d* is calculated. f it is due to the use of some special preparation I would orry no further, but if it is an extreme example of the working f the system of costing then there is perhaps room for further hought.

According to my own calculations, if, as is usually done, oth isoniazid and P.A.S are given in a combined cachet, the eekly cost for both drugs is unlikely to exceed 10*s* There is f course some economy here with only one dispensing fee for he combined preparation.

Birmingham Chest Clinic. V H SPRINGETT

SIR,—I was interested to read that the cost of treating Vilson's disease with penicillamine amounts to about 750 a year Previously I had been under the impression hat phenylketonuria was the most expensive disease

Provision of diet low in phenylalanine for the treatment of phenylketonuria involves the use of a special preparation of asein hydrolysate from which certain aminoacids have been removed and others added, together with some essential minerals A special vitamin preparation is also required. The treatment costs approximately £1 per day Dr Miller and Dr Smith very rightly draw attention to the overall economy when expensive preparations such as these are dispensed from a hospital rather than from a private pharmacist.

Alder Hey Children s Hospital,
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F P HUDSON

THE BRAIN AS A CLOCK

SIR,—I was glad to see that Dr Gooddy (Dec 26) had written again about the brain viewed as a clock. He is right about this, and it is valuable to have the statement reiterated What he is saying in effect is that there is a perceptual time and a public time which is agreed on by common consent, but that the two are never identical There are similarly perceptual and public dimensions of space

It might be objected that he is stating the obvious and insisting then on going on to explain it, but this would be a shallow, superficial view of the problem, for underlying Gooddy's proposition lies not any trite aphorism but a crucial enigma of existence In this as in other respects our brains are finite machines sampling a non-finite material We assume without the slightest justification that time has meaning apart from our private time, and that it is uniform throughout the universe This is ridiculous and unjustified, as by ordinary astronomical observation it leads to the absurdity of a constantly expanding universe Why not a contracting time—which would lead to a convergent time-point (with infinitely extended space and velocity) and would then presumably overshoot into an expanding time with constantly contracting space and slowing velocity? This would lead back to the primordial atom—which is, according to half of our physicists, where we started from

In all these *apparently* absurd ideas Gooddy's clock is one of the few firm points We could build machines which would not only indicate the passage of time but note it as well We could give them variable goal-seeking circuits and we should have non-living analogies with our own minds Unless we appreciate the fact that the mind has such a finite substratum we shall never begin to understand or overcome the exact nature of its limitations What Gooddy's clock stands for is the pendulum of our neurophysiological age He is ahead of his time—if there is a time

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ERIC TURNER.

HODGKIN'S DISEASE A MATERNAL-TO-FŒTAL LYMPHOCYTE CHIMÆRA?

SIR,—This new approach by Dr Green and his colleagues (Jan 2) to the ætiology of Hodgkin's disease is an interesting one, particularly to me, as it attempts to utilise some aspects of the immunological theory of cancer As with other attempts of this nature the authors have sensed the general idea but misunderstood the nature of the antigens believed to be concerned The "identity proteins" thought to be lacking in the cancer cell are the tissue-specific substances recognised by immune techniques as tissue-specific antigens These, which are almost certainly lipoprotein complexes, are located in the microsomal fraction and very probably in the endoplasmic reticulum We[1 2] shall shortly be presenting further evidence that this is the region where carcinogens may specifically operate

Now in their paper on Hodgkin's disease Dr Green and his colleagues are throughout discussing homologous or iso-antigenic immunity—i.e., the antigenic difference between individuals of a mixed strain. It is true that the work[3] on which my views were originally based seemed to show that carcinogens modified a cell component so as to make it iso-antigenic and therefore treated by the body as "not self" It was this property which led to the idea[4–6] that a similar modification might occur in surface tissue-specific antigens resulting eventually in an immune adaptation by loss of the modified antigen Iso-antigens are common to all cells of one individual and could not be primarily concerned in an often organ-specific process like carcinogenesis Their role in the homotransplantability of tumours is another story closely related to tissue transplantation in general.

Assuming that the lymphomas in radiation chimæras are the result of immunological aggression of either donor or host lymphocytes towards each other, what is a possible mechanism? We are dealing here primarily with homologous immunity, and iso-antibodies formed by donor cells would be absorbed by any type of host cell, including of course lymphoid cells, and give rise to the symptoms of homologous ("runt") disease, but this, according to my theory, would not be directly related to tumour formation. It is, of course, possible that antibodies may be formed against lymphatic tissue-specific antigens as a result of a homologous challenge just as antibodies are formed after heterologous challenge Whether produced by recipient or donor lymphocytes or both, the result could be similar in that neoplasia of either type might ensue This is supported by the finding[7] that lymphomas arising from either type do occur in irradiation chimæras

Whether or not such explanations are valid remains to be seen What does seem clear is that immune reactions play some part, for lymphomas arise only in chimæras produced by homologous, and not by isologous, injection of bone-marrow Moreover the similarity in the effects of homologous disease and of lymphoid tumours both in man and animals[8] is too close to be dismissed lightly as a chance relationship

My reason for writing is firstly to congratulate the authors of the communication on an ingenious idea, and secondly to try and make clear one aspect of the immuno-

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1 Green, H N *Acta Unio Internat Contra Cancrum*, 1960 (in the press)
2 Westrop J W, Green, H N To be published
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4 Green H N *Ann N Y Acad Sci* 1957, 68, 268
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logical approach to cancer It should perhaps be pointed out that I have made an approach [9] to the ætiology of tumours of childhood and early adult life by speculating that they were the result of failure of certain cells to acquire complete tolerance during fœtal life

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H N GREEN

THROMBOTEST METHOD FOR THE CONTROL OF ANTICOAGULANT THERAPY

SIR,—There are two main factors to be considered in the choice of a method for the control of anticoagulant therapy firstly, the results of the method should be reasonably correlated with the patient's tendency to bleed, and secondly, the method must be technically simple and rapid Of the present methods the prothrombin and proconvertin (P & P) method of Owren and Aas [10] fulfils the criteria better than any other This method has not gained the widespread popularity it deserves mainly because many small laboratories lack the staff and facilities for making the reagents Since the total number of patients receiving anticoagulant drugs is likely to rise, it is essential that a good method of control be available to all units both large and small

The thrombotest method recently introduced by Professor Owren (Nov 7) appears to fulfil this need He claims that the method is superior to the P & P method, as it is sensitive to both the intrinsic and extrinsic coagulation systems, whereas the P & P method is sensitive only to the extrinsic system The method is extremely simple, as only one reagent is necessary and this is available commercially in a freeze-dried form, also the method can be applied to capillary blood, whole citrated blood, or citrated plasma

I have recently had the opportunity to test three commercial batches of this reagent and to compare the method with the P & P method using the blood of patients receiving anticoagulant drugs The brief details of the technique are as follows

CONCENTRATION (%) FOR PLASMA FROM LUSTEROID TUBES

Case	Batch 27	Batch 28	Batch 30
1	10·5	8·0	7·6
2	11 5	10·0	10·0
3	18 0	18 5	20 0
4	13 0	13 0	8·6
5	20 0	20·0	17 5
6	10·0	9·0	7·4

(1) The ampoule of freeze-dried material is reconstituted with distilled water if capillary blood is to be used, or with weak calcium chloride solution if citrated venous blood or citrated plasma is to be used

(2) 0 1 ml of the appropriate blood sample is added to 0·5 ml of the reagent in the waterbath at 37°C

(3) The clotting-time of the system is recorded

(4) The result is read as "percentage activity" from a dilution curve supplied with each batch of reagent

As the method was found to be very sensitive to glass contact activation, Owren recommends that all blood samples (except capillary samples) should be collected in 'Lusteroid' tubes The dilution curves provided are for whole blood only, therefore if citrated plasma is used it must be diluted before testing by adding three parts of plasma to two parts of 0 85% sodium chloride solution

The first stage of the investigation of the method was to check the dilution curves supplied with the material For three batches of reagent, it was found that dilution curves made on whole blood and on plasma collected in siliconed or lusteroid tubes agreed very closely with the dilution curves supplied. The clotting-times of the dilutions were very slightly longer than those expected from the curves provided, giving results on abnormal test samples 1–2% higher than would have been obtained from the dilution curves provided with the reagent These dilution curves have since been found to be in error Owren [11] on rechecking has found that his dilution curves do in fact agree very closely with mine

Dilution curves prepared from whole blood or plasma collected in ordinary glass tubes gave results rather different from those provided The clotting-times of the diluted samples, although more variable than the siliconised samples, were

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9 Green, H N *J chron Dis* 1958, 8, 123
10 Owren, P A, Aas, K. *Scand J clin Lab Invest* 1951, 3, 201
11 Owren, P A Personal communication, 1959

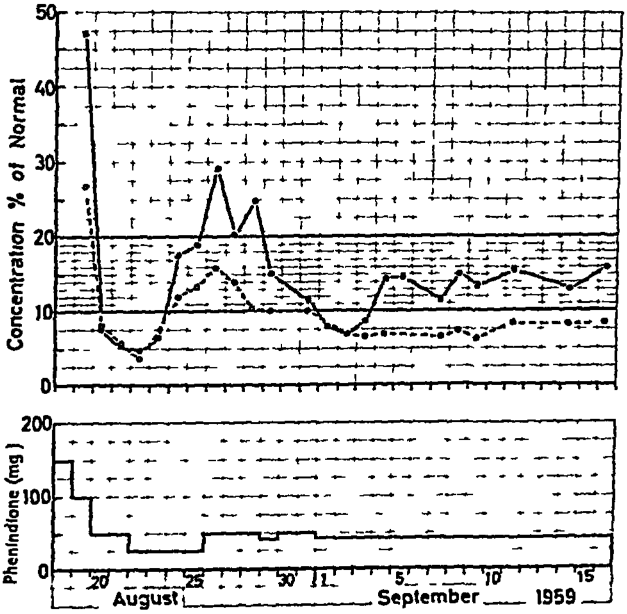

Fig 1

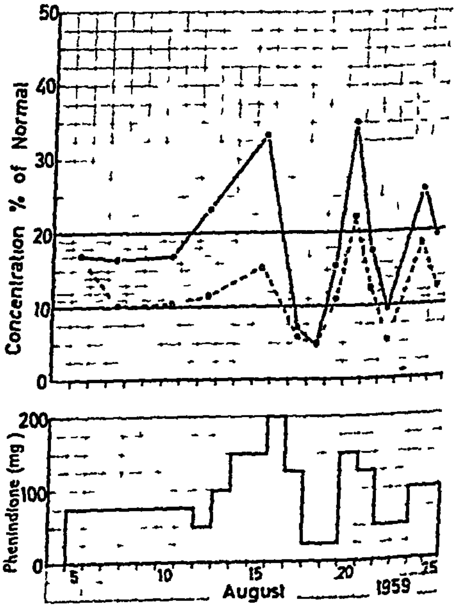

Fig 2

●———● P& P method ●– – –● Thrombotest

Figs. 1 and 2—Comparison of thrombotest and P & P methods on patients receiving phenindione The parallel lines indicate the therapeutic range accepted for the P & P method in this laboratory nerally much shorter As test samples collected in ordinary ass tubes also gave variable and sometimes unpredictable sults, the remainder of the samples for the investigation were llected in silicone or lusteroid tubes

A short experiment was made to determine if each batch of agent gave similar results with blood from patients on anti-agulants The results for plasma from lusteroid tubes are ven in the table, whole blood in lusteroid tubes gave similar sults

Some 350 samples from patients on anticoagulants were mpared by the thrombotest method and by the P & P method he results in general showed very close agreement. Two amples are shown in figs 1 and 2 Fig 1 gives a good ample of a case in which the appropriate dose of anti-agulant was rapidly determined and a constant dosage main-ined, whereas the example in fig 2 illustrates the effect of ltering the anticoagulant dosage by large amounts It can be en from the examples that the two methods give basically the me result, except that the thrombotest method appears to be ss sensitive in the near-normal range Also the results appear be generally a little lower than the P & P method as carried ut in our laboratory It is a remarkable testimonial to the & P method that a modification of the original technique,[12] hich has never been compared directly with that of Owren, hould give results in such close agreement with the new ethod which is directly calibrated by Owren.

The thrombotest method is commendable for its xtreme simplicity and for the fact that three types of lood sample may be used It appears to be subject to nly small random variations, and the difference between arious batches of the reagent is negligible provided that iliconed or lusteroid tubes are used for the collection of amples The P & P method appears to be the more ensitive method in the near-normal range, probably ecause a 1-in-10 dilution of plasma is used in that test. The thrombotest method is affected by heparin, whereas he P & P method is not very sensitive to the heparin oncentration likely to be encountered in blood samples The thrombotest method appears to be a major technical dvance in the routine control of anticoagulant therapy, oth short and long term, though some large laboratories nay prefer the P & P method for its greater sensitivity in he near-normal range

Department of Hæmatology,
Radcliffe Infirmary,
Oxford

M J ALLINGTON

HÆMATOLOGY IN BRITISH HOSPITALS

SIR,—Many will agree with Professor Dacie, in his excellent article of Jan 2, that hæmatology should be recognised as a specialty which requires an organisation distinct from pathology and medicine Indeed, a decade ago, the following statement appeared in a leading article [13] of *The Lancet* " Today hæmatology can fairly claim any advantages obtainable from full specialist status "

In the large centres, at least, the hæmatologist and his staff ought surely to be allowed to confine their activities to laboratory and clinical hæmatology, because this alone is likely to keep them very fully occupied. Yet it appears that very few consultants have been appointed hæmatologists as such. Most of the advertisements one sees are for pathologists with an interest in hæmatology, and occasionally physicians with an interest.

An appreciable number of present-day hæmatologists were trained in their early postgraduate years as general clinicians, and it may well be that this is much more important than a training in other branches of laboratory medicine Ideally, of course, the wider the laboratory and general clinical training before specialisation in hæmatology the better, but the most important qualification for a consultant in hæmatology should be his extensive clinical and laboratory experience in hæmatology itself

Some hæmatologists who themselves are clinicians appreciate having a free choice of physician to consult when confronted with a difficult general medical problem. Under Professor Dacie's scheme, such a choice might prove to be restricted to one physician already on the staff of the hæmatology department.

In order to obtain maximum efficiency from a hæmatological unit in the ultimate service of the patient, I am sure that clinical hæmatologists should have their own laboratories and outpatient and inpatient facilities. These would ensure a satisfactory service for patients referred to them by colleagues for diagnosis, for treatment, or merely for follow-up While a few are already fortunate in having at least some of these facilities, there is no doubt much room for improvement in all hæmatological units

I am grateful to Professor Dacie for providing an opportunity for discussion of some of these problems

Department of Hæmatology,
The Royal Infirmary and
Royal Hospital, Sheffield

E K BLACKBURN

THE ABNORMAL APPENDIX

SIR,—I should like to recall an astonishing remark of the late Professor Sauerbruck in Berlin at an international postgraduate meeting He said that 96% of appendicitis can be cured by conservative treatment, but because of the remaining 4% we are obliged to operate on all the 100%

Düsseldorf

TH OLBERT

INTRATHECAL PHENOL AND RELIEF OF SPASTICITY

SIR,—May we answer the question posed by Dr Liversedge (Jan 2)? The idea was conceived in April, 1957, on hearing Dr Nathan read his excellent paper to the Association of British Neurologists on the treatment of pain with intrathecal phenol and the explanation he proposed as to how this method, originally suggested by Maher, achieved its effect After some very helpful conversations with Dr Nathan on the question of technique, we immediately started to select patients for this trial and to subject them to a period of treatment with relaxants and physiotherapy until we were certain that no further help from these methods could be achieved before we submitted them to intrathecal injections

The first patient was actually admitted for an intrathecal injection of phenol in February, 1958, but eventually elected not to have this experimental treatment. At her request she was treated with neurectomies and tenotomies, but was in hospital for over six months with little improvement. This underlined the necessity for finding a more simple and less time-consuming method of dealing with flexor spasms and spasticity and emphasised the great advantage of the method of treatment under discussion. The first patient in our present series to receive an intrathecal injection of phenol was thus treated in September, 1958, and as the method does not demand prolonged inpatient treatment we had already nearly reached the halfway mark in our series by March, 1959

In reply to Dr Lipton (Jan 2) our criteria for selection of concentrations of phenol in 'Myodil' have been as follows

5% was used once only, proving sufficient in a child of 2 with a cerebral diplegia.

$7^{1}/_{2}$% was used in ambulant patients with troublesome spasms and in whom severe spasticity was not a problem

10% was used in ambulant patients with spasms and incapacitating spasticity and little if any sphincter disturbance.

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12. Allington, M. J *J clin Path* 1958, 11, 62
13 *Lancet*, 1950, ii, 404

15% was used in the bed-bound who retained some voluntary power but no sphincter control

20% was used only in the total and irrecoverable sensory and motor paraplegia

London, W 1

Reginald Kelly
P Gautier Smith

SENSORY DEPRIVATION

Sir,—Some recent work by non-psychiatric disciplines may widen the scope of your leading article of Dec 12

The psychiatric observations on sensory deprivation, begun in 1954 at McGill,[1] have been followed up independently in other departments of the same university, and it is now apparent that the need for adequate sensory nourishment is not just an isolated phenomenon of the "higher" centres, but is rooted deep in the brainstem Prof B D Burns, of the department of physiology, has shown in a most elegant and convincing manner how the respiratory centre itself, so long thought to be the possessor of an intrinsic tonic activity, is no exception to the rule that something must come in before something can go out, for when deprived of an adequate traffic of afferent stimuli its motor activity ceases[2]

In the department of anæsthesia we have been able to demonstrate a similar pattern of response at a lower spinal level Activity of the phrenic reflex arc (centre c3, c4, c5) is readily abolished by blockade of afferent stimuli up to a spinal level of T1[3] Presumably the mechanism is the same in both cases—a vital reflex activity can sleep quietly in its den if the total "pool" of neuronal visitations through and past its doors is inadequate to awaken it.

Perhaps the dysphoric feelings which arise during sensory isolation are merely a wholesome reaction attempting to supply an essential commodity from within when outside sources fail

Department of Anæsthesia,
Royal Victoria Hospital,
Montreal

P R Bromage.

TOLBUTAMIDE AND ANGINA PECTORIS

Sir,—In your issue of Dec 19 Professor Inder Singh and Professor Bardhan describe the beneficial effect of tolbutamide in angina pectoris, as observed in diabetic and non-diabetic patients

We have studied the effect of carbutamide on the electrocardiogram in 4-hour experiments, in diabetic and normal subjects (3 g orally) and in pancreatectomised and normal dogs (0 5 g per kg intravenously)

We observed in *all groups* a considerable reduction in heart-rate, which was not related to the changes in blood-glucose and serum-potassium levels In animal experiments we found a 30–50% decrease in heart-rate, which could be averted by bilateral cervical vagotomy or administration of atropine

In the animal experiments we observed in most cases a transitory inversion of T waves and a prolongation of the QTc intervals These phenomena took place both in hypopotassemia and during infusion of KCl, they were not related to blood-glucose levels, and they could not be influenced by vagotomy Vagotomy could modify T-wave inversions after carbutamide, but carbutamide given 1 or 24 hours after vagotomy caused the same T-wave inversion as in the normally innervated heart The same applied to the QTc prolongation.

These data[4] [5] seem to indicate that E C G changes after carbutamide may be partially due to the effect of the vagus nerve, but a direct effect on the myocardium cannot be excluded

We are aware of the fact that *acute* changes taking place after carbutamide administration cannot be compared with results achieved by chronic treatment with small doses of tolbutamide But (1) carbutamide is a cumulative drug, (2) it is used mostly by older patients in whom the danger of cumulation is greater, (3) determinations of plasma levels of carbutamide are not performed routinely, and (4) in older diabetics the myocardium is frequently not intact so we think that the occasional heart complaints and the E.C.G s of patients treated with carbutamide should be regarded very carefully

1st Department of Medicine,
University Medical School,
Szeged, Hungary

S Szűcs
G Csapó
A Tiszai

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[1] Bexton W H Heron, W, Scott, T H *Canad J Psychol* 1954, 8, 70
[2] Burns, B D Salmoiraghi G C *J Neurophysiol* (in the press)
[3] Bromage, P R *Canad Anæsth Soc J* 1958, 5, 29
[4] *Acta med Hung* 1959, 14 81
[5] *Z exp Med* (in the press)

TREATMENT OF BLEEDING PEPTIC ULCER

Sir,—The problem of acute gastrointestinal hæmorrhage, recently discussed in your columns, draws attention to the need for early diagnosis A ward barium meal using a mobile apparatus[1] has been used in the study of 200 patients admitted with hæmatemesis to the General Infirmary at Leeds in the period 1956–58 This method, which does not disturb the sick patient, is simple to carry out, unassociated with complications, and has yielded positive diagnostic information in a high proportion of patients studied[2]

It is reassuring for the surgeon to know the site of bleeding, enabling him to carry out a planned procedure, and directs attention to a specific lesion, thereby saving time which might otherwise have been spent in searching for the bleeding site

St Vincent's Hospital,
Dublin

Dermot F Cantwell

AUTOIMMUNE HÆMOLYTIC ANÆMIA DUE TO PHENACETIN AND *p*-AMINOSALICYLIC ACID

Sir,—We read with interest the article of Jan 2 by Dr MacGibbon and her colleagues We have recently encountered a somewhat similar case where the causal drug appeared to be salicylazosulphapyridine ('Salazopyrin')

The patient was a married woman of 26 years being treated for ulcerative colitis She was receiving a second course of salicylazosulphapyridine (1 g three times a day) when after three weeks of this therapy it was noticed that her hæmoglobin level had fallen from 10 6 to 8 g per 100 ml Investigation of her anæmia revealed microspherocytes, a reticulocyte count of 10%, and absence of haptoglobin from the serum. The urinary urobilinogen was increased but the serum bilirubin remained at 0 4 mg per 100 ml Neither Heinz bodies nor lupus-erythematosus cells could be demonstrated, and the direct antiglobulin test was negative Examination of the serum, however, showed it to contain a factor which in the presence of either salicylazosulphapyridine, sulphapyridine alone, or sulphamethazine was capable of sensitising both the patient's red cells and normal red cells from a donor of the same group, agglutination occurring at low dilutions of antiglobulin serum The antiglobulin test remained negative after the patient's cells had been incubated with sodium salicylate and patient's serum, and with salicylazosulphapyridine and normal serum

It seems therefore that the autoantibody mechanism may also be responsible for some of the hæmolytic anæmias induced by sulphonamides In the two cases of drug-induced autoimmune hæmolytic anæmia reported by Dr MacGibbon and her colleagues the direct antiglobulin test was positive, but in our case the test was negative The performance of an indirect antiglobulin test on the patient's serum with the addition of the suspected sensitising agent may therefore be of diagnostic value in the investigation of acquired hæmolytic anæmia

Coventry and Warwickshire Hospital
Coventry

N K Shinton
C Wilson

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[1] Cantwell, D F *Brit med J* 1957, ii, 911
[2] Cantwell, D F *Clin Radiol* 1960 (in the press)

GÖDEL'S PROOF

SIR,—Your article on Godel's proof (Jan 9, p 107) was interesting and important but it did not fully work out the psychological implications

Gödel's proof implies that human reason is incapable of achieving a watertight proof of its own rationality, even in the strict language of formal logic. The obsessional, however, demands absolute certainty, he is unable to accept the truth of Gödel's theorem.

Your article suggests that an obsessional would be cured if he could be made to accept a dogma and that the cultivation of a transference relationship establishes the analyst as an acceptable source of dogma. Surely if this happens the patient is not cured but merely has replaced one set of dogmas by another and still remains fixed to the delusion that absolute certainty can be reached by human thought.

This may be the reason why some analyses are so long, the analyst makes himself a source of dogmas so is unable to dissolve the transference relationship satisfactorily, the patient desiring the source of dogma never to dry up

The only cure for this is for the analyst to cure himself of his own obsessions and so cease feeding the patient with dogmas The analyst will then be free to tackle the more basic problem of the obsessional—which is, why does he demand absolute certainty

London, W 1

J M HEATON

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—Dr Simpson (Dec. 12) is to be congratulated on his excellent paper and follow-up of cavernous hæmangiomata and, judging by previous correspondence, it seems that the lesson to be drawn from his study has still to be learnt

I cannot see why it should be necessary to interfere surgically with a lesion which is going to disappear spontaneously without leaving a trace, as is the fate of the overwhelming majority of these lesions Atrophy, hæmorrhage, and ulceration have, in my experience, been extremely rare and usually occur only when the lesion is awkwardly situated (such as in the napkin area, but even there I have found that complications can generally be avoided by proper care) or when the lesion is of unusual size. I would agree with Mr Denis Browne (Jan 2), however, that surgery is the only satisfactory method of interference with these lesions, and I consider that radiotherapy is *never* justified

I have seen several cases of radiodermatitis following treatment of these lesions, and this is not at all surprising if doses of the order of 1800r are given in the treatment of these lesions, as would seem to be the practice of Dr Colin-Jones (Jan. 2) and his radiological colleague Most dermatologists now consider doses in excess of a total of 1000r, whether given in one dose or several, run the risk of producing radiodermatitis, with skin atrophy, telangiectasis, and disordered pigmentation, and ultimately of carcinomatous change.

Apart from this, we must consider the genetic risks associated with radiotherapy in childhood, and if it is true that a single quantum of X-rays is sufficient to produce a mutation in the germ cells of mammals, including man, then radiotherapy should be reserved for those conditions in which it is the only treatment or for patients in the post-reproductive epoch

There would seem to be very few conditions where radiotherapy of dermatoses is necessary in childhood and cavernous hæmangiomata are certainly not numbered among these

I am very surprised to learn from Dr Colin-Jones that these lesions are common in adults I had the opportunity during the last war of inspecting well over 100,000 airmen, and I cannot recall having seen *a single cavernous hæmangioma amongst them* In fact, apart from sclerosing hæmangiomata, which have a very different ætiology, I cannot recall, in sixteen years' dermatological practice, a single case of these lesions persisting into adult life, indeed, I cannot remember a single case in which the lesion had not disappeared by puberty

I am sure that it is only by careful study such as Dr Simpson has carried out that we are going to be able to show conclusively that very few of these lesions, when left alone, will give rise to any real disability, and that they in fact do spontaneously disappear

If a decision is made to interfere after a lesion has been present for an arbitrary period then we would never know their true fate, and I am sure that Mr Denis Browne will agree that Dr Simpson has made a contribution towards the true understanding of the natural history of these lesions and seems to have established beyond reasonable doubt that the overwhelming majority of these lesions do, in fact, spontaneously disappear, and further that the residual defects are few and rarely disfiguring

Surgery inevitably carries a risk with it, if only of an anæsthetic death, and a life lost in the removal of what is only a cosmetic blemish and never one imperilling life would seem to be a life lost for no very good reason.

Parents and relatives are apt to exert pressure on the family doctor because they do not like the look of the lesion, but I have found that careful explanation of its nature and its inevitable tendency to disappear spontaneously *sooner rather than later*, helps to keep up their morale pending this happy result.

I consider it would be a most retrograde step in the management of these lesions if once again these children are to be submitted to radiotherapy, with all its potential genetic consequences—apart from the risk of subsequent radio-atrophy and, even, carcinoma—or to unnecessary surgery, and I hope that every dermatologist who has closely followed his cases will publish his experiences

Dr Simpson is following in the footsteps of Dr Lister in the West Country, who, more than twenty years ago, persuaded dermatologists to leave these lesions alone We now have to educate the recalcitrant few who still interfere with them and to teach the surgeons that Nature nearly always achieves better results than they can, although we may need their help and be grateful for it in the very exceptional case.

Guy's Hospital,
London, S.E 1

E J MOYNAHAN

SIR,—The fact that these lesions disappear spontaneously after some years is an argument against dangerous or mutilating treatment but not against treatment of any kind

Occasionally treatment is indicated by the location of the lesion as on the eyelid or lip The complications of hæmorrhage, ulceration, and infection with resultant scarring are uncommon but such a nuisance when they occur that they are worth avoiding Above all these hæmangiomata are disfiguring, children can be very frank about blemishes on each other and many a child, untreated, will reach an age in which unhappy embarrassment will be caused. Most of all, consider the mother whose delight and pride in her baby includes its physical appearance, the firm reassurances of the doctor may prove right in the end but do not prove the blemish is not there—there to stay for some years

Application of carbon-dioxide snow for fifteen seconds will quite abolish a small superficial lesion and will gradually improve nearly all the rest Those who use this treatment may find it so simple, safe, and effective that one wonders why anyone should want to withhold it.

The Middlesex Hospital,
London, W 1

F RAY BETTLEY

Sir,—*Primum non nocere* first not to harm In other words, never write " Operation successful, patient died " Or, as we must regard the deaths on M1 as justified in the interest of speed, are we to regard carcinomas as justified in the interest of that other modern idol, cosmetics? We should not be swayed towards potentially dangerous treatment by occasional doubts of natural resolution

Summerfield Hospital,
Birmingham ROBERT J HETHERINGTON

CASE-FATALITY IN TEACHING AND NON-TEACHING HOSPITALS

Sir,—The further contribution (Jan 16) from the social medicine research unit at The London Hospital is a welcome stimulus, but of course will arouse ill-informed lay, political, and medical political opinion It would be very helpful to know, particularly in the prostate series, whether the case-fatality rate was at its height in night emergency operations In the period under survey this had become an exciting new adventure for the average registrar

The N H S covers its deficiency with respect to emergency services by saying that there is a surgeon " on call " He may live 20 miles from the hospital, have perhaps three sessions a week or less at the hospital, and yet be expected to provide non-stop service day and night for one week in three For years we have waited for a solution to this problem, and still we wait for the working party's report After that we shall wait for action upon the report With the emergency service of the country undertaken largely by overworked registrars, many of whom have been trained outside the British Isles, it is little wonder that the case-fatality rate is higher than it ought to be In many places the registrar is in fact more skilled than his consultant supervisor in some of these emergency procedures, but it is judgment that is perhaps more important than craft skill in prostatectomy

What has been said about surgery applies equally to the night anæsthetic services in the non-teaching hospitals

London, S E 19 D F ELLISON NASH

WITHHOLDING OF SICKNESS BENEFIT

Sir,—Mr Hervey's experience (Dec 19) of the withholding of sickness benefit has also been mine, although the delay in submitting the medical certificate was a matter of only a few days—not that the length of time should make any difference I gave a sound matter-of-fact reason for the unavoidable delay, but it was not, of course, accepted and a protest was followed by typewritten foolscap sheets bearing copies of the correspondence, with an invitation to appeal against the decision if I wished

The official forms warn the intending suppliant (I am sure this is the only word to use when dealing with any department of Government) who hopes to attain his rights that any delay in submitting the certificate(s) *may be* followed by a withholding of benefit if an adequate reason is not given for the delay The difficulty is that nobody has ever been able to discover what *is*, in the opinion of the local manager (or whoever it is who makes these arbitrary decisions to refuse payment), a good reason for *not* refusing payment, if indeed there *is* a good official reason. This is a dark bureaucratic secret But one suspects that the words "may be" are a Governmental euphemism for " will be "

Any attempt to obtain redress is made so cumbersome by the necessity to appear before an "appeal court" to show cause why you think you ought to receive your just deserts that you cannot help thinking it is done deliberately to discourage you. I believe that the strategy is generally successful, but in any case one has no confidence that the decision will be reversed and the matter is allowed to slide as a waste of time and effort, either because of illness or because, when you have returned to work, you are too busy to spare the time on what you are certain is a foregone conclusion.

If bureaucratic chicanery is denied and no suspicion or charge of dishonesty is held or preferred against the medical profession or the public, then the Minister should state, without verbal woolliness or equivocation, *why*, in the name of common sense or even of honesty, payment of benefit should not be made, no matter what the length of the delay in the receipt of the certificate

Folkestone. B G EDELSTON

HOTELS OR HOSPITALS?

Sir,—Mr Stallworthy's deduction (*Jan 9*) *that* convalescent hospitals would result in economies appears to be based on a misunderstanding of the meaning of present methods of hospital costing The policy would not reduce the cost of the hospital service and would, in fact, slightly increase it as the following argument shows Let the convalescent annexe be built adjacent to the corresponding acute block, the cost will not be more than if it be built at a distance and will, in fact, be less because some of the services can be shared with the acute hospital Now let a door be made between the acute and convalescent wards, will this increase the cost of either? Looking at the problem the other way round, the cost per bed of the hospital keeping convalescent cases in acute wards is derived from the cost of the first few days of admission (high), and the cost of the later period of stay (low) Remove the patient at the point between these stages and the cost per bed of the acute hospital will automatically rise in proportion

The way to reduce the cost per patient treated lies in other directions which Mr Stallworthy has also indicated these include providing services such as radiology, pathology, operating-theatre space, &c, only to the level required by the acute cases and ensuring that patients are not kept in hospital longer than is absolutely necessary

Convalescent wards always disrupt the nursing continuity and the medical continuity on the resident staff level. Experience sadly teaches that it also breaks the consultant continuity because visits to convalescent wards tend to be rare and mainly to clear beds This creates a " dump " where patients suffer from too little clinical activity The whole conception of postoperative transfer to convalescent wards is thoroughly undesirable on clinical grounds But most importantly it is a further heavy blow to the already atavistic doctor-patient relationship in our hospitals

The Royal Infirmary,
Sunderland D A SANFORD

Sir,—I have read Mr Stallworthy's article with great pleasure It is an excellent contribution to the thought that is needed if money on new hospitals is to be well spent

Mr Stallworthy writes as director of a gynæcological unit and believes that hospital treatment of medical and surgical patients could be carried out more economically and at least as effectively as at present if acute hospitals were smaller and were supplemented by convalescent annexes He gives experience from the department of gynæcology of the United Oxford Hospitals to support his belief and asks for an experimental pilot trial in which doctors, nurses, and administrators could test the plan for different types of hospital work and find the advantages and disadvantages

Once large ideas such as these enter the mind other important questions arise. How many patients are better for hospital treatment and by how much are they improved? Is the attention of hospital doctors too much concentrated on surgical and medical techniques to the neglect of other means of improving patients' wellbeing? Can the prevention of diseases be hastened by closer collaboration of general practitioners, hospital doctors, public-health doctors, and research-workers?

These problems are being studied in other countries and the rebuilding of hospitals is a good opportunity to study them here Our patients are showing an interest in these matters A few months ago, the Duke of Edinburgh challenged us in his presidential addresses to the Canadian and British Medical Associations to take a wider interest in the health—rather than the illness—of the community

London, W 1 J M ALSTON

ÆTIOLOGY OF LEUKÆMIA

SIR,—The letter of Jan. 9 by Dr Nowell and Mr Hungerford was most interesting Whether or not autonomy of *acute* leukæmic cells is specifically indicated by an abnormal chromosomal pattern, abnormalities in the chromosomes of *chronic* granulocytic leukæmia are—in my opinion—not in contradiction with the theories exposed.

Secondary alterations in the "chronic" cells' genetic material are apt to arise sooner or later on these cells' way to ultimate autonomy

Gorinchem N H D SCHOYER.

BREECH PRESENTATION AND DELIVERY

SIR,—In your leader of Jan 9 you do not make a strong enough case for the abolition of external cephalic version before labour

In this hospital White[1] reported a 5% fœtal mortality associated with this manœuvre, and from 1950 to 1956 652 versions were attempted amongst 9681 deliveries In 480 of these cases in which this was performed without anæsthesia, the mortality due to version was 1 (0 21%) and in 172 cases with anæsthesia 3 (1 7%) During this period there were 119 uncomplicated breech deliveries with 2 deaths (1 6%) In spite of these 652 attempts at version in this clinic, the incidence of breech presentation is 2 6%

Steptoe and Moore[2] reviewed 50,255 deliveries and found the incidence of breech delivery to be 2 8% when external cephalic version was never performed (before labour)

The safety of version is irrelevant since it often cannot be shown that it significantly reduces the incidence of breech presentation

Obstetric Hospital,
University College Hospital,
London, W C.1 J D MARTIN

SIR,—Your leading article states

> "The need for cæsarean section in breech delivery will vary from one hospital to another Hospitals deal with selected clinical material, and the rate of cæsarean section will depend on the ages, stature, and parity of the patients and the weights of their babies and is likely to be high when there are many emergency admissions Study of a total community would give a much truer picture of the management and results of breech presentation in any particular area, and would make valid comparisons possible Unfortunately, there is at present little enthusiasm for such an epidemiological approach to obstetrics"

The results of 1 2%-corrected fœtal loss, in association with a cæsarean-section rate of 16% as reported by Hay[3] for St. David's Hospital, Bangor, could in fact be used as a basis for such an epidemiological study The Bangor figures represent as closely as it is possible to visualise what can be expected in "any particular area" or "total community" from a highly organised area obstetric service. This statement is based on the following facts

(1) St David's Hospital is the only fully equipped maternity unit serving the counties of Caernarvon, Anglesey, and Merioneth The population catered for is 215,000 Because of geographical position and the hospital's popularity it is unlikely that many cases from the area are delivered outside the region

(2) 75–80% of all pregnant women in the area are supervised antenatally at ten peripheral clinics and three hospital clinics by medical personnel based at the main hospital at St David s

(3) 84% of all cases in the area are delivered in hospital—either at the main hospital or in the five peripheral general-practitioner hospitals

(4) All cases of previously undiagnosed breech presentation arriving at the peripheral hospitals are referred to the main hospital

(5) In the area there is a very high standard of cooperation between the general practitioners, district midwives, and the hospital staff, and all breech presentations seen on district are, where possible, referred to the main hospital for delivery

It is unlikely, therefore, that in the area there are many cases of breech presentation who do not ultimately come under the hospital's supervision.

St. David s Hospital, Bangor, North Wales DAVID HAY

ATYPICAL HAPTOGLOBIN PATTERNS IN TUMOUR PATIENTS

SIR,—I should like to add some further comments to my preliminary report of Nov 28

I have now learnt that the sera of cancer patients have an increased haptoglobin concentration, and thus the atypical components are intermediary complexes depending on partial saturation with hæmoglobin

Uppsala. LARS BECKMAN

CONTROL OF ANTICOAGULANT THERAPY

SIR,—In their evaluation of the new reagent, thrombotest, Dr Matthews and Dr Walker (Dec. 26) estimate the cost of each test to work out at about 4*d* (p 1162) A direct approach to the Norwegian source of supply on the other hand yields a quotation at the widely disparate figure of 1*s* 8½*d* Such a price, if sustained, renders an otherwise quite admirable preparation uneconomical for general use

Dumfries and Galloway Royal Infirmary,
Dumfries J LAURIE

TREATMENT OF INGUINAL HERNIA

SIR,—In their valuable though depressing article of Jan 16 Mr Shuttleworth and Mr Davies show that the Bloodgood operation gives good results, though the numbers are small. I assume, perhaps wrongly, that they mean the rectus-sheath flap technique first described by W. S Halsted[1] and first used by him four years earlier Bloodgood's own remarks[2] were, "Later Halsted modified the transplantation of the muscle by turning down a pedunculated flap of the anterior sheath of the rectus"

In 1952 I followed up 78 inguinal herniæ in 68 patients All operations had been carried out by me, using the rectus-sheath flap technique, and all follow-ups involved personal examination by myself at intervals varying from 2¼ to 11 years The ages of the patients lay between 26 and 74 years There were 5 recurrences, a recurrence-rate of 6 4%, this includes 1 patient whose original site was sound but who had a bulge at the margin of the rectus muscle and another whose original site was sound but who had a femoral hernia on that side when seen 10 years later There was 1 recurrence among 10 bilateral herniæ, this was at the site of operation for a recurrent hernia following an operation 18 years earlier There were no recurrences among 20 direct herniæ.

Dissatisfied with a recurrence-rate of 6 4% and impressed by Tanner's description of the rectus-sheath slide technique, I abandoned the so-called Bloodgood method some years ago, but the St. Thomas's figures indicate that it is still a valuable procedure to remember when assessing the condition found at operation

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[1] White N L *Brit med J* 1933, ii, 364
[2] Steptoe T T, Moore, W T *Sth med J*, *Nashville*, 1943, 36, 295
[3] *J Obstet Gynæc Brit Emp* 1959, 66, 529

[1] *Johns Hopk Hosp Bull* 1903, 14, 209
[2] *J Amer med Ass* 1918, 70, 515

Leicester DONALD McGAVIN

INCUBATION PERIOD OF CUTANEOUS LEISHMANIASIS

SIR,—In his valuable article on Jan 16, Professor Symmers refers to the variable and sometimes prolonged incubation period of cutaneous leishmaniasis (oriental sore)

Perhaps I may be allowed to emphasise this point by mentioning that an interval as long as four years and seven months has been reported as elapsing between experimental human inoculation and the appearance of the lesion,[1] and that naturally occurring cases with circumstantial incubation periods of five [2] and even ten years [3] have been recorded

Portsmouth and Isle of Wight Area
Pathological Service,
Central Laboratory, Portsmouth R D CLAY

PRENATAL ORIGIN OF THE RESPIRATORY DISTRESS (HYALINE-MEMBRANE) SYNDROME OF PREMATURE INFANTS

SIR,—Attention has been drawn to the presence of a substance, probably a mucoprotein in the lungs, which greatly reduces surface tension when the area lined by it is reduced during expiration[4] This prevents excessive collapse of the lungs before the beginning of the following inspiration, and thus promotes stability of lung expansion A significant reduction of this activity is found regularly, though not exclusively, in the lungs of newborn infants dying with the respiratory distress syndrome (sometimes called hyaline-membrane syndrome)[5] This makes available for the first time a tool for the systematic and objective study of at least some of the aspects of this puzzling condition

The following observations were made on a group of stillborn infants who had not lived to show either the clinical signs or the pathological changes characteristic of the syndrome

They were among 120 perinatal deaths in which static pressure-volume curves were obtained from lung specimens Air was introduced at pressure increments of 2 to 5 cm of water up to 30 cm, and further increments of 5 to 10 cm, usually up to a point where further increase did not significantly enlarge the lung volume Pressure was then decreased by similar steps Each experiment took from 15 to 30 minutes, and was repeated at least once In about one-third of the cases lung extract was subsequently examined by means of a variable-area surface balance by Clements and coworkers, there was good correlation of surface-tension data with the stability of lung expansion.[6]

For the purpose of greater ease of evaluation of the stability of expansion, a method was devised which characterises the shape of the deflation curve between 10 and 0 cm. of water pressure by the area between it and the abscissa, in relation to the level of maximal expansion A high figure denotes good stability, most values ranged below 1 2 A description of the calculation, and detailed evaluation of all results in stillborn and liveborn infants, will be reported elsewhere

The lungs of most infants dying with the respiratory distress syndrome showed poor stability, which is in agreement with Avery and Mead.[5] The question now arises whether the deficiency in surface activity observed in the respiratory distress syndrome is present at birth, or arises after birth under the influence of the early stages of the syndrome or a predisposing condition. In other words, one wonders whether a newborn infant may be destined or predisposed to develop the respiratory distress syndrome before taking its first breath

STABILITY OF LUNG EXPANSION OF 38 STILLBORN INFANTS

Stability figure	Body-weight							Total
	Up to 500 g	501–1000 g	1001–1500 g	1501–2000 g	2001–2500 g	2501–3000 g	Over 3000 g	
0 00–0 10	—	1	1	—	—	—	—	2
0 11–0 20	—	—	—	—	—	—	—	0
0 21–0 30	—	3	—	1	—	—	—	4
0 31–0·40	—	1	—	1	—	—	—	2
0·41–0 50	—	2	1	—	—	2	—	5
0 51–0 60	1	—	1	—	—	—	—	2
0 61–0 70	—	—	—	—	—	1	—	1
0 71–0 80	—	—	—	—	—	—	—	0
0 81–0·90	—	1	—	—	1	1	1	4
0 91–1 00	—	2	—	—	2	—	2	6
1 01–1 10	1	—	1	1	—	—	1	4
1 11–1 20	—	—	—	2	2	1	—	5
1 21–1 30	—	1	—	—	—	1	—	2
Over 1 30	—	1	—	—	—	—	—	1

The accompanying table shows the stability of lung expansion for all 38 stillborn infants within the present material It is apparent that the values are not uniformly distributed, but form a low-stability group below 0 7 (16 cases) and a high-stability group above 0 8 (22 cases), each with its own peak. No values between 0 7 and 0 8 were observed Poor stability occurs frequently but not uniformly in the very immature, it was not found in infants weighing more than 3000 g The incidence of low stability in relation to birthweight appears to follow approximately the trend of occurrence of the respiratory distress syndrome Microscopic examination of the stillborn material showed no difference between those with low and those with high stability

Differences in the stability of lung expansion therefore exist in infants who have never breathed This suggests that an infant may be predisposed to the respiratory distress syndrome while in utero We do not know whether infants born with good stability can, as a result of some disease process, yet develop the syndrome The present evidence suggests, however, that at least some of the causative factors should be looked for in the intra-uterine environment or in the intrinsic constitution of the fœtus It is interesting to note that the latter possibility has been suggested by Lieberman[7] on the basis of absence of the activity of the plasminogen activator

This work was aided by a grant from the United Cerebral Palsy Research and Educational Foundation

Departments of Obstetrics and Pediatrics,
Johns Hopkins University, Baltimore PETER GRUENWALD

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—For those who work in hospitals without facilities for blood-transfusion, autotransfusion can be a life-saving measure as your correspondents have confirmed I learnt this the hard way in the 'thirties when in Hong Kong where ectopic gestation was a common disease It still is in many parts of the world where blood-transfusion services do not exist In an article[8] entitled " Aids in the diagnosis and treatment of ectopic gestation " I emphasised the value and ease of autotransfusion The " citrate " method was used and the blood, provided it was not infected, scooped out of the abdomen with a galley-pot and filtered through 6 layers of fine gauze By this means, not only were lives saved but convalescence was much more rapid

University College Obstetric Hospital
London, W C.1 W C W NIXON

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1 Berberian, D A *Arch Derm Syph, Chicago*, 1944 50, 231
2 Latyshev N I, Kojevnikov, P V, Povalishina T P Borovsky's Disease (Cutaneous Leishmaniasis), p 32 Moscow, 1953
3 Clay, R D, Ross A A *Brit med J* 1956 i, 1279
4 Clements J A, Brown, E S, Johnson R P *J appl Physiol* 1958, 12, 262
5 Avery, M E, Mead J *A.M.A J Dis Child* 1959 97, 517
6 Clements J A, Hustead R F, Johnson, R P, Gribetz, I (to be published)
7 Lieberman J *New Engl J Med* 1959, 260, 619
8 *Brit med J* 1937, i, 579

Obituary

ERIC HENRY RHYS HARRIES

M.D. Lond., F.R.C.P., D.P.H.

As medical superintendent of fever hospitals in Birmingham and London during the 'twenties and 'thirties, Dr E. H. R. Harries did his most important work when the acute infectious diseases were prevalent and had a heavy mortality. An expert in diagnosis and treatment, he was also a pioneer in administrative and technical methods of control. He died on Jan. 12 on his 78th birthday.

He qualified from the London Hospital in 1906, and after holding the post of R.M.O. at Tite Street Hospital for Children, Chelsea, he entered the fever service as a medical officer at Fazakerley Hospital in Liverpool. He left to take up a post as tuberculosis officer under the Welsh National Memorial Association at Newport, Monmouthshire. During the 1914–18 war he served with the R.A.M.C. in Mesopotamia. In 1920 he became medical superintendent of the Birmingham Fever Hospital.

At Birmingham he realised the potentialities of immunisation, and he was an early advocate of immunising all children against diphtheria and nurses against scarlet fever and diphtheria. This work attracted the attention of Dr J. A. H. Brincker, then in charge of the London County Council fever hospitals, and in 1931 Harries was appointed superintendent of the North Eastern Fever Hospital (now St Ann's General Hospital, Tottenham). It had 661 beds and was the largest fever hospital in constant use in the L.C.C. service. Harries quickly gave the North Eastern the facilities of a general hospital. He introduced radiology, and in those days, when mastoids were one of the worst complications of scarlet fever, radiology was a valuable guide to treatment. He also encouraged the use of electrocardiography in his diphtheria wards. Though he was a pioneer of immunisation against scarlet fever he realised its imperfections and welcomed wholeheartedly sulphonamides, and later penicillin, as well as an efficient streptococcal antitoxin, as means of reducing the stay of children in hospitals. He was particularly interested in mechanical measures to alleviate diphtheritic tracheitis.

His Milroy lectures to the Royal College of Physicians in 1935 were a masterly analysis of current practice in the control of infection in children's wards and the dangers of cross-infection. At a time when complications were rife he tried to lessen them by bed isolation, limitation of visitors, masking of patients, treatment of carriers, passive immunisation of patients (especially against measles), and active immunisation of nurses. In his pioneer work in 1933 on scarlet fever he showed that active immunisation did not increase the number of carriers. All these methods improved the lot of children, but, as he once said, " no degree of architectural skill, no medical administrative measures, and no elaboration of technique can prevent entirely the transference of infection by human agencies. The best laid schemes may fail unless in addition the personnel is numerically and technically adequate to cope with the special dangers of infection which must inevitably attend the aggregation of children in hospitals."

Harries in due course succeeded Dr A. F. Cameron as chief medical superintendent of the fever hospitals of the L.C.C. and he took a prominent part in designing a new type of ward block for the reconstruction of his hospital. He retired in 1947.

At Birmingham he had been the lecturer in infectious diseases, and in London students from the Middlesex and Royal Free Hospitals attended his courses. His book, *Clinical Practice in Infectious Diseases*, written with the late Maurice Mitman, was first published in 1940 at a time when the control of infectious diseases was of national interest. The orderly arrangement, lucid writing, and good sense shown in this work were also evident in his counsel as a consultant adviser to this journal.

A. D. writes:

" Harries had a quick and original mind and the uncanny knack of exposing the core of a complex problem with lightning speed. He was tall and thin. He took life seriously and was renowned for his caustic wit: it was woe betide any junior at his hospital who became slack. Apart from a liking for music, he made his work and his patients his hobby and had no other. He was an omnivorous reader—a taste which he was able to indulge after his retirement."

Dr Harries was president of the Medical Officers of Schools Association in 1938–39. Of his work there R. E. S. writes:

" He kept abreast of progress and was always willing to help with his experience. He spent many hours helping us to revise our code of rules as well as presiding at our meetings. He was always ready to advise members who wished to immunise schoolboys and he always pointed out the snags as well as the advantages. No pressure would ever make him accept a fee: he said simply that he was full-time. He usually looked in a hurry and frail, but he always found time to do the things he thought were worth while."

Dr Harries leaves a widow and two children. His son is neurosurgeon to University College Hospital.

ISABEL EMSLIE HUTTON

C.B.E., M.D. Edin.

Lady Hutton, emeritus consultant psychiatrist to the British Hospital for Functional Nervous Disorders and the author of several well-known books on health education, died at her London home on Jan. 11.

She was the only daughter of James Emslie, deputy keeper of the Privy Seal of Scotland, and she was educated at Edinburgh Ladies' College and the University of Edinburgh, where she qualified in 1910. After postgraduate study in Vienna and Munich, in 1912 she took her M.D. with honours in psychological medicine and later held appointments as pathologist at Stirling District Mental Hospital and the Royal Mental Hospital in Edinburgh. During the 1914–18 war she served with the Scottish Women's hospitals in Macedonia and Serbia and the Lady Muriel Paget Hospital at Sebastopol. For her work she was awarded the Serbian orders of the White Eagle and St. Sava, the French Croix de Guerre, and the Order of St. Anne of Russia. After the war she returned to her Edinburgh appointment, but she resigned it on her marriage in 1921 and settled in consultant practice in London. She was appointed to the staff of the West End Hospital for Nervous Diseases and the British Hospital for Functional Mental and Nervous Disorders, where she held outpatient clinics for early mental cases. This work led her to write her book on *Mental Disease in Modern Life*. Her experience with outpatients also led her to write *The Hygiene of Marriage*, first published in 1923, which ran into nine editions. In 1958 she published *Woman's Change of Life*.

In 1938 Dr Hutton moved to India, where her husband held an appointment at Quetta. During the late war she was director of the Indian Red Cross Welfare Service, and she held this post until 1946 when she returned to this country and resumed her practice in London. She was appointed C.B.E. in 1948.

L. F. writes:

" Isabel Emslie as a girl must be a still vivid memory to many of her contemporaries at Edinburgh University for her spontaneous charm and gay courage All medical women in those days had to face a rough passage, worse after they qualified, and Isabel Emslie had just the necessary qualifications for this sort of pioneering Her sunny good looks and good temper smoothed away many of the initial difficulties, and she steadily refused to let the most obstinate prejudice get her down Such opportunities as came she made the most of The basis of her professional work was a great desire to help other people in trouble, especially those who tended then to be neglected, and it was this driving force that impelled her to take up psychiatry and apply her experience for the benefit of women in neurotic difficulties In both world wars Lady Hutton's gifts of initiative and organisation found full scope, first in the Balkans and later in India In the end she remained a gracious, sympathetic, stimulating personality, loved and admired by a wide circle "

Lady Hutton is survived by her husband, Lieut-General Sir Thomas Hutton

Public Health

Scattered Cyanide

LATE at night on Monday, Jan. 11, three containers of potassium-cyanide powder fell into the roadway at Ashby Parva, in Leicestershire, from a haulage contractor's lorry travelling northwards to Leire One of the containers was broken open and about 25 lb of its contents spilled into the highway The police and fire brigade were called and the undamaged and open containers removed The powder on the highway was hosed away into roadside gullies and through the farmyard of Long Acre Farm adjoining the highway in Ashby Parva. The effect of hosing the powder from the highway was to convey a toxic solution into gullies, which discharge into open ditches and thence into watercourses, and on to the surface of the highway, the farmyard, and the adjacent field Accordingly, all householders in the affected area were warned not to use well water and to withdraw cattle and stock from the open fields

Meanwhile, a representative of Imperial Chemical Industries Ltd , acting for the manufacturers of the powder, had arranged for the supply of a strong neutralising agent and this was applied in the early afternoon of Jan 12 to the gullies, highway, farmyard, and field From the chemical reaction obtained it was obvious that this treatment was effective, but there could be no assurance that all the toxic liquid was reached, and in fact samples taken from the farmyard and field in the late afternoon of Jan. 12 showed traces of the poison. Samples taken earlier from five wells showed no trace A further application of the neutralising agent was made on Jan. 13

There was a blocked road gulley in Ashby Parva, and arrangements were being made for this to be released under control and washed out with neutraliser Meanwhile tests continued to be taken at all points to which it seems possible that the poison could travel

All affected authorities and public utility undertakers were informed, and the Trent River Board gave considerable assistance in the field analysis of samples The Ministry of Housing and Local Government sent a senior engineer and a chemist to advise on any further steps which might be taken

It will not be possible for some two or three weeks to say with certainty that there is no danger to public health, but during this time the inhabitants of the area affected or likely to be affected will be told not to drink from private wells and to keep cattle and stock away from ditches and watercourses It is hoped that this action will cause only minor inconvenience, since there is a public supply of piped water throughout the area.

We are indebted to Dr A C Ross, medical officer of health, Blaby Rural District Council, and to the Clerk of Lutterworth Rural District Council for supplying this information

Diary of the Week

JAN 24 TO 30

Monday, 25th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P.M Mr N W Please Elements of Statistical Methods
MANCHESTER MEDICAL SOCIETY
9 P.M (Medical School, University of Manchester) *General Practice* Dr Richard Stone Treatment of Diabetes
UNIVERSITY OF ST ANDREWS
4 P.M (Queen's College, Dundee) Mr R D Muckart Posture

Tuesday, 26th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P.M *Medicine* Dr Philip Ellman, Prof A C. Lendrum, Dr A I G McLaughlin Pulmonary Hæmosiderosis
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M (London School of Hygiene and Tropical Medicine Keppel Street, W C.1) Prof R J V Pulvertaft Autoimmune Reactions
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M Mr Alistair Gunn Fœtal Behaviour
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P.M Dr J N Milnes Neurology
INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W C.1
5 P.M Dr Josef Warkany (Cincinnati) Teratology and *Pædiatrics*
INSTITUTE OF DERMATOLOGY, Lisle Street, W C.2
5 30 P.M Dr R. M B MacKenna Ætiology of Pruritus and its Management.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P.M Sir Ralph Marnham Some Rectal Complaints
ROYAL STATISTICAL SOCIETY
6 15 P.M (London School of Hygiene and Tropical Medicine) *Medical Section* Dr R. S Doll Mechanisms of Carcinogenesis—Epidemiological Evidence
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Dr L A Liversedge Writer's Cramp
UNIVERSITY OF ST ANDREWS
5 P M (Queen's College, Dundee) Dr H B Goodall The Buffy Coat in Hæmatological Investigation

Wednesday, 27th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C.2
5 P M (Arnott demonstration) Dr D H Tompsett Preservation and Injection of Anatomical Material
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr Rosemary Biggs Treatment of *Hæmophilia*
INSTITUTE OF DERMATOLOGY
5.30 P.M Dr R W Riddell Fungi Causing Skin Disease
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W.3
5 P.M Mr O S Tubbs *Use of Heart-lung By-pass and Deep Hypo*thermia in Cardiac Surgery
WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 P M. (Rembrandt Hotel, S W 7) Detective Chief Superintendent J Smale *The Relationship Between Doctor and Police*
MANCHESTER MEDICAL SOCIETY
4.30 P.M (Medical School, University of Manchester) *Medicine and Pathology* Prof D V Hubble Steatorrhœa
ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW, 242, St Vincent Street, Glasgow, C.2
5 P.M Prof P B Medawar Immunology of Transplantation. (Lock lecture)
UNIVERSITY OF ST ANDREWS
2.30 P.M (Queen's College, Dundee) Mr I M Stewart Bone Replacement

Thursday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M Lieut -Colonel J C Watts *Missile Injuries in Cyprus* (Hunterian lecture)
UNIVERSITY OF LONDON
5 30 P.M (School of Pharmacy, 29 Brunswick Square, W C.1) Prof F Blanquet (Bordeaux) Ion Exchange Resins and Thyroid Metabolism (First of two lectures)
BRITISH *POSTGRADUATE MEDICAL FEDERATION*
5.30 P.M (London School of Hygiene and Tropical Medicine) Dr R. G White *Immune Cellular Reactions*
INSTITUTE OF DERMATOLOGY
5.30 P.M Dr A D Porter Photosensitivity
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Hospital, Oxford
8.30 P M Mr R. G Taylor, Mr J R. Gleave Injuries to the Cervical Spine
MANCHESTER MEDICAL SOCIETY
8 P.M (Staff House, University of Manchester) *Anæsthesia* Dr I Hallack Fluid Balance and Anæsthesia Dr B J Muir Anæsthesia in a Children's Burns Unit
UNIVERSITY OF ST ANDREWS
5 P.M (Queen's College, Dundee) Prof A L. d Abreu *Progress in* Surgery of the Heart and Great Vessels

Friday, 29th

UNIVERSITY OF LONDON
5.30 P.M *(School of Pharmacy)* Professor Blanquet Ion Exchange Resins and Thyroid Metabolism (Second of two lectures)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M Mr R. L. Holt Trends in the Surgical Treatment of *Peptic Ulceration*
4 P.M Mr Please Elements of Statistical Methods
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road W C.1
5.30 P.M Dr T V L Crichlow Cholesteatoma and Marginal Disease
INSTITUTE OF NEUROLOGY, National Hospital Queen Square W C.1
4.30 P.M Dr E. A Carmichael Studies of Hemiplegia of Early Onset

Notes and News

EXCHANGES BETWEEN RUSSIA AND THE UNITED STATES

ONE of the most welcome breaches in the Iron Curtain, agreed in principle during Mr Krushchev's visit to the United States in September, is the exchange agreement between the United States and the Soviet Union. Its medical section includes plans for cooperation in the next two years. The programme wisely provides not only for exchanges at Ministry level (between the Soviet Ministry of Health and the U S Public Health Service) but also between specific research institutes and individual workers. It also provides that the Governments should facilitate publication of articles by workers of each nation in the journals of the other and increased exchange of medical journals, books, and films.

More specifically, cooperation is planned in research on cancer (between the Soviet Institute of Experimental and Clinical Oncology and the American National Cancer Institute and Sloan-Kettering Institute), on cardiovascular disease (between the Soviet Institute of Therapy and the American National Heart Institute and, through them, other bodies), and on poliomyelitis (between the Soviet Institute for the Study of Poliomyelitis and, in America, the Research Foundation of the Children's Hospital in Cincinnati, where Dr Albert Sabin has his laboratory, and the National Institutes of Health). The bodies concerned will give each other information about past research and future plans, exchange specialists, organise joint studies, and take part in annual meetings alternately in the United States and the Soviet Union. This year the studies on poliomyelitis will concentrate on the Soviet use of the Sabin live-virus vaccine, and the meeting will be held in the Soviet Union, the meetings on cardiovascular and malignant disease will be held in the United States.

Other exchanges planned are of parties of up to 20 senior and junior research-workers for periods of up to a year to learn about the work of scientific establishments in the other country, to exchange experience, and to conduct joint research, and of smaller delegations for a few weeks to study specific subjects. Soviet delegates in the United States will study neoplasms, especially biochemical and histochemical research, cardiovascular pathology, especially hypertension and ischæmic diseases, cardiac surgery and methods of artificial circulation, virus genetics, and industrial hygiene, especially silicosis, industrial toxicology, and the physiology of labour. American delegates will study microbiology, neurophysiology and neuropathology, metabolism and genetics, medical ecology, and maternal and child care, especially any data that can be added to the U S Public Health Service study of 40,000 mothers and their children before and six years after birth for factors influencing congenital defects.[1]

TEACHING NUTRITION

THE major nutritional diseases are fortunately now rare in most countries of Europe, but few doctors could claim that they have no worries about the state of nutrition of some of their patients. Some kind of governmental food policy, backed by the best advice, is needed in even the richest countries. In democratic countries, since national policies tend to follow public opinion, it is obviously important that everyone should understand about food and know what is needed: this requires teaching, or even preaching, and the medical profession has an important part to play.

In December W H O and F A O held at Bad Homburg, near Frankfurt, a joint symposium on Education and Training in Nutrition in Europe. Perhaps the most interesting proposals concerned teaching in medical schools.

> " It was made clear that the training of medical students in nutrition is inadequate in many medical schools. Although many of the basic and clinical aspects are taught, there is a lack of integration between the various disciplines, moreover, the subject is not taught as a practical subject related to everyday problems of family life. In order to remedy this, one person could with advantage be made responsible for the co-ordination of all aspects of nutrition teaching at all stages of the medical student's career. He should be a person who has a comprehensive and practical knowledge of nutrition."

One proposal was that the necessary coordination could be achieved by the establishment of a " nutrition unit ", attached to an existing department and staffed by members specially interested in nutrition who should have facilities for laboratory and field research and also for teaching.

The report of the symposium, to be published in French and English, will also deal with the education in nutrition of public-health officers, medical postgraduates, nurses, dietitians, nutritionists, home economists, agronomists, and schoolteachers.

University of Cambridge

On Dec. 22 the degree of B CHIR. was conferred on the following:

C L C Arnold, N A Atalla, N J Barton, J P Blackburn, David Bond, F M Boston, K R Bowles, E. G Cantrell, A F S Childs, R. B Church, D R F Clark, T T Davies, J B Douglas, G H. Evans, E W L Fletcher, C du Ve Florey, D M C Forster, H B Francis, F R. Gamman, N F C Gane, David Godwin, John Gough, S G I Hamilton, Simon Harcourt-Webster Alexander Harley, T S Hattersley, J M Henk, Pamela M. Hill, Peter Hill, G A. Hobbs, G R. Hobday, S M N Jaikaran, E V Jones, R S Kirk, J E R. Lart, Beng Kwan Lee, R A Lewin, P W Lord, J E D MacLaren, J H MacMillan, D M. Marsh, N J Maurice-Smith, C S Menzies-Kitchin, R H Morgan, D N E Myers, M J Orrell, Margaret E Peppercorn, J N Powell, D A Richards, E. H Richards, Shirley J Richmond, J R. L Roberts, A P Sherman, R I R Sinton N J Strickland, Michael Thomas, P G R Tingley, Keith Whittle, J S Wrigglesworth

University of Bristol

At recent examinations for the degree of M.D the following were successful:

T J Butler (with distinction), C C Downie, J E Tovey

University of Sheffield

A course in dermatology for general practitioners will be held on April 4–8 at the Rupert Hallam Department of Dermatology, Sheffield Royal Infirmary. Further details may be found in our advertisement columns.

University of St. Andrews

On Jan 8 the following degrees were conferred:

M.B , Ch.B—Mary R Bestow, Catherine D Campbell, B C Davies, Doreen Wilson or Eldred, A M Gough, S W Gray, A B A Grubb, James Lawless, *G A Nimberg, R. C Waters, Assefa Woldesemait

Ph D in the faculty of medicine—* Deva Nandan Sharma

* In absentia

University of Glasgow

On Jan. 16 the following degrees were conferred:

M.D—E. McC. McGirr, R. G Sommerville (with honours), A. P Curran, Robert Rankine, Morag C. Timbury (with commendation)

Ph.D—G C. Arneil

Ch.M—D W Short.

M.B , Ch.B—J G Bisset, J T Breen, J M. Carlisle, T A. H Hide, E. J N Hoisington, James Kelly, Alexander King, J L. Kydd, Charles Lynch, Margaret M McNamara, G L Miller, G A. Montgomerie, John Newlands, T P Orr, Patrick Palmer, W H. Pitt, Thomas Prior, G D Ross, Lingasphara Lutchmana Venkatasawmy, Jean M West, Hannchen D Wirth.

Order of St. John of Jerusalem

The Queen has sanctioned the following promotions in, and appointments to, this order:

As Knights—William Bain, M.B , Brigadier Sir Kenneth Fraser, C.B.E., E.D , M.B , F.R.A.C.S., R. S Steel, O.B.E., M.B., M.R.C.P , F.R.A.C.P , Major-General Sir Frank Norris, K.B.E., C.B., D.S O , E.D , M.D , B C. Cohen, M.B., Brigadier A. L Dawkins, O.B.E., E.D , F.R.C.S., A.A.M C.

As Dame—Mary A C. Ainscow, M.B

As Commanders (Brothers)—P S Pringle, M.R.C.S., Air Commodore John Magner, M.D , E. L. Butler, M.B., W L. Stewart, M.B K M. Macdonald, M.B , Robert Rutherford M.B., T.D , W R. Cambridge, M.R.C.S , Lieut.-Colonel E J Selby, O.B.E., M.R.C.S., S G Nelson, M.B., F.R.C.P , F L. Firkin, M B , Major Brooke Moore, M.B., F.R.C.S., Lieut.-Colonel George Gregg, O.B.E., M.D , F.R C.P

As Officers—A J Amor, C.B.E., M.D , J W McK. Nicholl, M.D , D I Acres, M.R.C.S., Wing-Commander H. W Whittingham, M.B., K G Bergin, M.D , J L. Temple, M B., F.R.C.S , W H Dunn M.R.C.S., Sukha Sagar Datta, M.D , Alexander Burns, O.B.E., M.C., M.B , D K. Gaitskell, M.R.C.S., Surgeon Commander H M Darlow, M.R.C.S., R.N , Salvino Caruana, M.D , H G Vyse, O.B.E., M.R.C.S., J S McLintock, M.B , M. A. Byer, O.B.E., M.B., C. D Bateman, M.B , Henry Gordon Prest, M.B., L. D Hodby, M.B., A. N Jacobs, M.B , Elizabeth M Anderson, M.D , Mary E. Rolston, M.B

Royal Society

An award under the society's and Nuffield Foundation's Commonwealth bursaries scheme has been made to Dr J C Gould, senior lecturer in bacteriology, University of Edinburgh.

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[1] *New York Times*, Dec 16, 1959

Royal College of Surgeons of England

At a meeting of the council on Jan 14, with Sir James Paterson Ross, the president, in the chair, Mr L J Williams was admitted to the court of patrons Prof A W Wilkinson was admitted to the fellowship *ad eundem*

Mr H J Seddon was appointed Robert Jones lecturer, and a Moynihan lectureship was awarded to Prof Fernand Orban and a college lecture to Mr Douglas Robb (Commonwealth travelling professor) Dr R P W Shackleton was appointed Frederic Hewitt lecturer for 1961

The following diplomas were granted jointly with the Royal College of Physicians

D I O—Unus Omar Ali, Soroj Kanto Ally, G P E Beaney, Leslie Bernstein, P R Blenkinsop, D J Durcan, Muriel E Gibb, Sujit Kumar Guha, D G Jones, J G Kourris, Ram Partap Kumar, G J Little, R S McAlary, W J O'Connell, Iraj Parhizgar, A S Shalom, O T Taylor, C I Woolf

D A—R St J Angel, Raja Ghulam Asghar, Avadhut Vishnu Bal, Shirley B Barker, R S B Bennett, A I Booth, J P Broad, J M B Burn, N F A-Byam, Anne L Campbell, F N Campbell, J L Canton, Charlotte L K Christie, Doris W Cole, Maeve S Counihan, J W Crooke, Eileen M Darwood, I C Dixon, M P Dowdell, I S du Toit, H B Edghill, Pamela E Fancourt, D J Foley, Ann F Gamble, June S Grant, A M Hall Smith, Pamela C Harrison, J J Hazlett, Hla Tun, R F Hunt, J L Hunter, Elizabeth M Irvine, K C B James, F W Jones, V R Keep, Anne H Kinnell, Onkar Krishna, W van der M Lambrechts, Doreen J Leckie, Muriel F Lehane, D B Longson, B M Lottering, Elizabeth M B McKenzie, Kailash Chandra Mathur, J A Monro, J D Muir, J J Mulcahy, P C Murray, Pamela M Mylward, Sidhanand Sadashiv Nadkarni, Badrudeen Gulamhusain Nanji, M A Ness, Elizabeth M Nicholson, M P O'Dwyer, Sheila M Power, Prem Narain Rastogi, Marian J Rice, K W Ridings, D S Robertson, Audrey F Rogers, Shefali Roy, Vivienne Schein, H G Schroeder, M D Scott, Sein Sein Khin, Gursharan Kaur Singh, Davangere Hiremutt Sivadevaiah, Janet M Spencely, Pamela J Stow, M B Teal, J G Teall, A T Thomasson, Elizabeth M Thyne, B le G Waldron, Edith J Wilson, Kathryn M Wilson

D M R D—Sabah Al-Fakhri, M A Bloomfield, A L Brown, Stephanie J Carter, Khuen Wai Chow, J O M C Craig, J W Davidson, H F Davies, Sydney Elk, Nathan Geffen, A G Giddins, J B Howells, D I N Jayawardena, Roger Kayaleh, I H Kerr, J J Key, C D Krasner, Ramendra Nath Kundu, P M McIlrath, R H Mackay, L R MacLean, Lim Mak, G F Mayall, Mohamed Ismail Mohamed Nilar, R A Owen, J H Pell, Tekman Rajcoomar, M F Shellshear, J B Simmons, Elizabeth M Sweet, D H Trapnell, H P Tulloh, M J Turner, P J De La Rey Van Wijk, H R Watson-Baker, Vivienne Chong Ping Wong, J Chu Kee Yin

D M R T—Maung Tin Aung, Daphne I L Dacosta, Sinnathamby Kandiah Dharmalingam, R G B Evans, H T Ford, Emma Mukherjee, Prasert Nilprabhassorn, J P Perry, Urmil Sikand, Mary F G Skinner, Bin Cheng Tan, Yok Kuang Tan, Maung Myo Tint

D P M—G M Baird, Rashmohan Banerjee, D F H Beattie, R C Benians, R G Bird, V H A Black, J P Bomford, Anne N M Brittain, R A Brooke, Dorothy L N Brown, Elizabeth F Browne, D M Carter, J A Chapman, L G Cottrell, G O Cowdy, E W Davies, J D Denford, A W Drummond, Harry Eaton, Aaron Esterson, C L Finn, I G Fitz-Patrick, Joyce M Galbraith, R S Gillen, L J Glancy, Norman Gold, Elizabeth A Green, J A Gumbrell, Christina McI Hamilton, J A Harris, A R Jones, Norman Kaye, A V de P Kelly, John Le Gassicke, Janet M M Lindsay, D I M McNeill, J B McWhinnie, Barbara G Meyler, R T F Moloney, M C Moss, Richard Neville, C O Oshodi, P L Parsons, Arnold Pearce, J P S Powell, D J Power, Vikram Swarup Rastogi, M J Sainsbury, J F Scott, R W Smith, R F Steel, C D Thomson, K J Tilling, G C Timbury, N A Todd, H P Tollinton, Nancy M Tweedie-Stodart, D S Vorster, D G A Westbury, M T C Wright, Nicholas Wright, L M Zinkin

D Path—M D'A Crawfurd, J A McMillan, Abdul Salam Mohamed, Kazimierz Posney, Dona Priyalatha Wijesinghe

D P H—M W Beaver, Prasanta Kumar Biswas, Chamnong Boonmark, J K Butterfield, Carmelo Cassar, H A Collins, Dorothy M Edwards, C O Foenander, F W Ford, R McK Laslett, Sushila Maity, A A Opara Nadi, S F Nu Amu Otoo, D G H Patey, B A Roberts, Olujimi Akanbi Soboyejo, Anne Quee Cheng Tay, Anne M Timmis

D C H—P G Mendis

Postgraduate Medical School of London

A symposium on recent advances in knowledge of the anæmias will be held for consultants on March 25 and 26, and not on April 7 and 8 as previously announced Further particulars will be found in our advertisement columns

Preventive and Clinical Medicine for Older People

The Society of Medical Officers of Health and the British Geriatrics Society are holding a conference on this subject from March 31 to April 2 in Bristol Further particulars may be had from the secretary of the Society of Medical Officers of Health, Tavistock House South, London, W C 1

New M R.C Units

The Medical Research Council have lately set up a blood coagulation research unit, by agreement with the United Oxford Hospitals, at the Churchill Hospital, Oxford, under the part-time direction of Dr R G Macfarlane, and an environmental radiation research group under the honorary direction of Prof F W Spiers in the department of medical physics, University of Leeds

Griseofulvin Symposium

A symposium on the oral treatment of fungus infections will be held at 1, Wimpole Street, London, W 1, on Friday and Saturday, May 13 and 14 Particulars may be had from the symposium secretary, St John's Hospital Dermatological Society, St John's Hospital, Lisle Street, W C 2

Royal Society of Health

The annual congress of this society will be held at Torquay from April 25 to 28 under the presidency of Lord Morrison of Lambeth For the first time there will be a section of the executive councils' services, of which Dr R W Rae will be president Other sections will include health education (president, Dr Doris Odlum), medical officers of health (Dr J Stevenson Logan), preventive medicine (Dr G S Wilson), mental health (Prof G R Hargreaves), family health and welfare (Prof A B Semple), and hospitals (Dr G E Godber) Further particulars may be had from the press officer of the society, 90, Buckingham Palace Road, London, S W 1

Medical Art Society

This society's exhibition will be held from March 4 to 17 at Walker's Galleries, New Bond Street, London, W 1

The *Journal of the Faculty of Radiologists* is to change its title to *Clinical Radiology, The Journal of the Faculty of Radiologists* as from the January issue (vol 11, no 1) The change in title is accompanied by changes in cover design, typescript, and format, and the journal will now be published by Messrs E & S Livingstone Ltd, of Edinburgh

The Sheffield University Medical Society's annual dinner will be held on Thursday, Feb 4, at 8 P M in the Firth Hall of the university The principal guest and speaker will be Mr A Dickson Wright. Tickets (members 18*s* 6*d*, patrons 22*s*, non-members 25*s*) may be had from the dinner secretary at the university

A semipermanent exhibition on clinical effects of griseofulvin, arranged by Dr Brian Russell and Dr C J Stevenson, will be held at the Institute of Dermatology, Lisle Street, London, W C.2, from Feb 3 to 26

Appointments

ASHLEY, J B, M D Lpool consultant pathologist, Glantawe H M C area
CHAMBERS, ROBERT, M B Durh, D P M assistant psychiatrist (S H M O), Horton Road and Coney Hill group of hospitals, Gloucester
CORBITT, F H, M R C.S, D I M psychiatrist in mental deficiency, Greaves Hall Hospital, Southport
GOUGH, M H, M B Lond, F R C S part time surgical outpatient assistant The Hospital for Sick Children, Great Ormond Street, London
HINGSTON, C W J, M R.C.S, D.P H, D T M & H assistant M O (school health and child welfare services), Worcestershire
JONES, D H, M R C.S, D P M consultant psychiatrist and medical superintendent, Deva Hospital, Chester
LUNT, R L, M B Manc, M R C O G part time consultant obstetrician and gynæcologist, City General Hospital, Sheffield
McCARTHY, T F, M D, B SC Wales, M R C P consultant geriatrician, Glantawe H M C area
MACVICAR, DONALD, M D Edin, M R C O G part time consultant obstetrician and gynæcologist Royal Infirmary, associated maternity hospitals and General Hospital, Leicester
SPENCER, R W, M B Birm, M R C P consultant pathologist, West Cornwall clinical area
WATSON, W S, M D Edin, F R C P E, D P M consultant neurologist, department of surgical neurology, Western General Hospital and Royal Infirmary, Edinburgh

Newcastle Regional Hospital Board

DAVIES, G I, M R C S, D P M consultant psychiatrist in child guidance St Luke's Hospital, Middlesbrough
DUNCAN, G D, M B Aberd, D P H deputy S.A M O to the Board
MURRAY, FRANCIS, M.R C.S D P.M assistant psychiatrist (S H M O), Prudhoe and Monkton Hospital
VAITHILINGHAM, P S, F R C S senior casualty officer, Sunderland group of hospitals

Colonial Appointments

BECKER, M J J T, M.D Münster, D T.M & H psychiatrist British Honduras
CACHIA, Carmel, M D Malta, D T.M & H senior M O Kenya
COOPER, A S, M B Cantab, M R C P medical specialist superintendent Bahamas
NOEL, J D O, M B M O, Grenada
RAJAH, S G M M D M O, Mauritius
STRUDWICK, R H M B Birm, D T.M & H, D P H senior M O Kenya
TUBOKU-METZGER, A F, F R C P E, D T M & H senior specialist, Sierra Leone

The Lancet · Saturday 30 January 1960

SOME VIRUS ISOLATIONS FROM COMMON COLDS

I. EXPERIMENTS EMPLOYING HUMAN VOLUNTEERS

D. A. J. Tyrrell
M.D. Sheff., M.R.C.P.

M. L. Bynoe
M.B. Lond.

G. Hitchcock
B.A. Cantab

H. G. Pereira
Dr Med. Brazil

C. H. Andrewes
M.D. Lond., F.R.C.P., F.R.S.

From the Common Cold Research Unit (Medical Research Council), Salisbury, Wilts

Work on the common cold is hampered because it has not been possible to detect or propagate the causative virus or viruses except by inoculation of human volunteers or chimpanzees. In this and the following papers we describe some properties of the cold viruses under study at this unit, and evidence for their transmission in vitro. The first paper lays particular emphasis on experiments employing human volunteers and the second and third on some laboratory studies. It should, however, be made clear that the various lines of work have been artificially separated and were actually carried on in parallel.

Clinical Methods

Volunteers were isolated and observed at this unit by the methods previously described (Andrewes 1949, Roden 1958). They were isolated for 4 days before administration of the inoculum and were observed for 5 days after inoculation. The inoculum of 1 ml., diluted if necessary in Hanks' saline, was administered as drops up the nostrils. Assessments were made by a clinical observer unaware of the nature of the material under test.

Laboratory Methods

Tissue-culture Techniques

Human embryos from therapeutic hysterotomies performed between 3 and 5 months of gestation were dissected aseptically at the Royal Marsden Hospital. The kidneys and lungs were placed in a sterile bottle immersed in broken ice and sent to this unit by train. The renal cortex and medulla were chopped with sharp scalpels into pieces about 1 mm. across and placed in Hanks' saline. The tissue was washed and the cells were dispersed by treatment with 0·25% 'Difco' trypsin in Hanks' saline at 37°C and a pH of about 7·4. The cell suspension was removed and added to 5 ml. horse serum and the process repeated. The cells were spun down and resuspended in medium to give a final dilution of 1/100 to 1/500. The medium consisted of 5% or 10% calf serum and 0·5% lactalbumin hydrolysate in Hanks' saline containing 0·03% sodium bicarbonate and 100 units penicillin, 100 µg. streptomycin, and 20 units of nystatin (mycostatin) per ml. 1 ml. was added to culture tubes closed with silicone bungs. The tubes were incubated at 37°C without rotation and the medium was renewed every 2 or 3 days until a cell sheet was formed; this usually took about 5 days.

Human embryo lung cultures were prepared in the same way. Human thyroid cultures were prepared as described by Pulvertaft et al. (1959), calf kidney cultures and monkey kidney cultures as described elsewhere (Negroni and Tyrrell 1959). When ready for use, the cultures were washed with Hanks' saline and 1·5 ml. of medium 199 with the antibiotics mentioned above was added. 0·2 ml. of inoculum was then added, and the cultures were placed in a roller drum.

The medium was usually changed 1 day after inoculation and at intervals of 4 days thereafter if necessary. Incubation at this stage was either at 33° or 36°C.

In early experiments it was thought that cold virus in the fluids from cultures maintained in medium 199 was losing its activity on storage or after repeated freezing and thawing; thereafter 0·5% of bovine plasma-albumin, fraction V (B.P.A.),* was added to culture fluids before storage in the dry-ice refrigerator, and specimens were frozen and thawed only once.

The Virus Strains

From adults, not in isolation, with typical common colds, nasal washings were taken, using either 10% broth saline or Hanks' saline containing 0·5% bovine plasma-albumin, 100 units of penicillin and 100 µg. of streptomycin per ml. were added. The washings were shaken with glass beads and centrifuged at about 2000 r.p.m. for 10 minutes. After 1/10 dilution in broth saline or Hanks' saline they produced typical colds when inoculated into volunteers.

To exclude the presence of known viruses the washings were then introduced into tissue cultures—in early experiments HeLa cell and human embryo lung cultures were used. Later we turned to cultures of human embryo kidney and monkey kidney cells maintained in medium 199 and tested for hæmadsorption (Vogel and Shelokov 1957). Several passages were made and the total period of observation was several weeks. We found no evidence of the presence of known enteroviruses, adenoviruses, or the parainfluenza (hæmadsorption) viruses recently isolated from persons with respiratory diseases (see reviews by Huebner et al. 1958 and Andrewes 1959). Washings were stored in a dry-ice refrigerator at about −50°C and thawed immediately before use.

Results

Properties of the Viruses

We made a few observations on properties of the agent producing colds in volunteers, for reasons which will become apparent later in this series.

(a) Ether Resistance

Washings were mixed with from 10 to 20% by volume of diethyl ether and held at 4°C overnight. The ether was then removed and the washings were inoculated into groups of volunteers. Control material was prepared in the same way without addition of ether. The virus apparently survived ether treatment in 5 of the 6 washings tested. In the case of the P.K. pool of washings, 5 of 14 volunteers inoculated with ether-treated material developed colds while 6 of 14 inoculated with untreated material did so. With H.G.P. washings, the corresponding figures were 1 of 6 and 1 of 5.

(b) Acid Resistance

A washing containing strain H.G.P. was dialysed at 4°C for 3 hours against 0·1 M citrate buffer pH 2·1; the buffer was then removed by dialysis against saline. None of 7 volunteers who received this material developed colds, although 2 of 8 volunteers who received untreated material did so.

(c) Neutralisation by Human Serum

The strain of H.G.P. was used for experiments to determine whether a virus of this type could be neutralised by immune

TABLE I—NEUTRALISATION IN VITRO OF COMMON COLD VIRUS (STRAIN H.G.P.)

—	No. of colds in volunteers receiving washing mixed with				
	Broth saline	Acute phase serum*	Convalescent serum*	Bovine plasma albumin	Human γ-globulin
Experiment I	3/8†	2/10	1/10		
Experiment II	3/9			3/10	0/18

* The sera were obtained from subject H.G.P. at the time the washings were taken and 16 days later.
† Numerator = no. of colds. Denominator = number of volunteers inoculated.

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* Supplied by Armour Laboratories, Hampden Park, Eastbourne, England.

serum Acute and convalescent phase sera from the donor of the washings were heated at 56 C for 30 minutes, diluted 1 in 10, and mixed with an equal volume of washings diluted 1/5 The mixtures were held at room-temperature for about 2 hours before inoculation to volunteers In a second experiment the washings were mixed with an equal volume of a solution of Lister Institute human γ-globulin 10 mg per ml and held at 4 C overnight and then at room temperature for 2 hours A control containing bovine plasma-albumin was also used The results are shown in table I The serum did not neutralise the virus but the γ-globulin apparently did so Since the bovine albumin did not neutralise, it is probable that the effect of the γ-globulin was due to its content of antibodies The results and conclusions are similar to those of Jackson et al (1958)

Propagation of Virus Early Attempts

Andrewes et al (1953) reported an apparently successful attempt to transmit a common cold strain (D C) in roller-tube cultures of human embryo lung maintained in Enders' medium However, no colds were produced with material beyond the tenth passage and numerous attempts over 2 years to repeat the experiments were unsuccessful (Pereira and Roden, unpublished experiments) It seemed that some technical modification might hold the key to success Accordingly the method of organ culture was used No success was obtained using human embryonic œsophagus, skin, nasal epithelium, or intestine There was rather more promise with fragments of embryonic human trachea (see Bang and Niven 1958) A few colds did occur in volunteers inoculated with the first passage in such cultures The results were, however, irregular, colds could not be produced with material from passages beyond the first and it seems possible that the few colds were caused by virus surviving from the inoculum

Further experiments with roller-tube cultures of monkey kidney were then carried out We tried medium 199, Enders' medium (5% horse serum, 5% beef embryo extract, and 90% bovine amniotic fluid), and 0 1% yeast extract with 0 5% lactalbumin hydrolysate in Hanks' saline, and we varied the interval between passing Colds occurred infrequently and irregularly in volunteers receiving material from any of these cultures

An attempt was next made to repeat the experiment using human embryo kidney cultures Because of shortage of materials only medium 199 was used and the experiment had to be discontinued as the cultures began to disintegrate after 10 days in this medium Nevertheless material from these cultures produced colds in volunteers more frequently and the matter was therefore systematically investigated, as described below

Results with Modified Technique

The experiments were planned to determine as clearly as possible the significance of the colds in volunteers receiving human embryo kidney culture material They might have appeared because the inoculum enhanced nonspecifically a hypothetical latent cold virus infection in the volunteers This possibility was controlled by giving volunteers uninoculated culture medium containing bovine plasma-albumin at the time at which other volunteers received the test material

We also tested the possibility that there might be a cold virus latent in the tissue cultures, volunteers were given fluids from a parallel series of passages made exactly as in the test series except that it was started with uninfected broth saline The third possibility was that the volunteers might be infected by virus carried over from the original washing, to test this we gave fluids from passage series made in culture tubes without cells or in cultures of calf kidney cells, we thought it unlikely that cold virus would grow in calf kidney cells, yet these might nevertheless preserve the virus At first these control materials were given separately, but in later experiments they were pooled

The results obtained have been summarised in table II They show that no colds developed in 78 volunteers who received control material of various sorts, whereas 22 colds developed in 102 who received fluids from cultures inoculated with cold washings The differences observed for second-passage fluids, when the most strictly controlled trials were made, are statistically significant (P between 0 05 and 0 01) Taken at their face value these results suggest that both the P K and H G P cold viruses were transmitted in culture for two passages Virus probably disappeared by the fourth passages, unless we postulate that it multiplied in a form avirulent for man

TABLE II—COLDS PRODUCED BY INOCULATION OF VOLUNTEERS WITH FLUIDS FROM CULTURES MAINTAINED IN MEDIUM 199 WITHOUT SUPPLEMENTS

Strain	Passage	Temperature (C)	No of colds in volunteers receiving			
			Test fluid	Control fluids		
			Inoculated human cultures	Uninoculated human cultures	Inoculated calf cultures	Inoculated tubes without cells
P K	1	33 & 36*	4 9			0 8
P K	1	33	3 7			
P K	1	36	1 6			
P K	2	33	2 10			
P K	2	33	3 14	0 11		0 8
P K	1	33	0 7	0 5		
H G P	1	33 & 36	2 9			0 8
H G P	2	33	1 8	0 5	0 7	
H G P	2	33	5 16	0 8	0 8	
H G P	4	33	1 16	0 7		

* A mixture of fluids from cultures maintained at each temperature

Attempts were made to repeat these experiments using different materials Human embryo lung cultures were inoculated with P K virus, and human thyroid cultures were inoculated with the H G P strain The D C strain of cold used previously (Andrewes et al 1953) was inoculated into human embryo kidney cultures No colds were produced when first- or second-passage fluids from these experiments were given to groups of about 8 volunteers (22 volunteers in all), nor did any colds result when two groups of 10 volunteers received second-pass material from human kidney cultures inoculated with each of two "wild" cold washings which had failed to produce colds when administered to volunteers

Variations in Technique of Passage in Human Embryo Kidney Cells

We attempted to improve the method of cultivation by repeating these experiments systematically, varying the conditions and testing pooled or individual culture fluids in volunteers The results were not statistically significant but seemed to indicate that transmission probably occurred better at 33 C than 36 C, on harvesting at 1 rather than 2 or 6 days, and on transferring either medium or cell extracts

In-vitro experiments (Hitchcock and Tyrrell 1960) suggested that the virus might more readily be transmitted when 0 2% of B P A, and an extra 0 1% of glucose were added to the maintenance medium We therefore made serial passages in culture maintained in this medium starting with second-pass fluids of strains of H G P. and P K which had produced colds in volunteers The third strain, F E B, was passed at first in medium 199 supplemented with glucose and then with B P.A also In all cases the cultures were maintained at 33° in a roller drum, and passages were made at 5 days using the fluid phase only

Table III shows that volunteers inoculated with material from the third, fourth, and eighth tissue-culture passages developed colds, they were, however, infrequent in volunteers receiving H G P and P K material Altogether 14 of 71 volunteers who received virus material developed colds, while 3 of 55 who received control material did so This difference is statistically significant (P < ·05) and strongly suggests that something was being transmitted which could cause colds in man This conclusion is however mainly due to the results obtained with strain F.E B material, and it is possible that the other two strains became attenuated on passage The significance of our findings is discussed at the end of the third paper in this series (Tyrrell and Parsons 1960)

TABLE III—COLDS PRODUCED BY INOCULATION OF VOLUNTEERS WITH FLUIDS FROM HUMAN EMBRYO KIDNEY CULTURES MAINTAINED AT 33 C IN MEDIUM 199 SUPPLEMENTED WITH BOVINE PLASMA ALBUMIN AND OR GLUCOSE

Strain	No of serial passages	No of colds in volunteers receiving		
		Test material	Control material	Saline
H.G.P	4 8	2/16 2/15	1/12 1/10	0/5
P.K.	8	1/10	1/11	
F.E.B	3 4 8	3/6 2/8 4/16	0/7 * 0/6	0/4

* 5 volunteers, one of whom developed a cold, have been excluded because the inoculum given was found to be contaminated with Echo 11 virus

Summary

We have studied nasal washings from adults with common colds The causative virus in 5 of 6 washings was not inactivated by ether treatment. One strain (H G P) was tested further and found to be inactivated by human γ-globulin and by treatment at pH 2

Certain virus strains apparently survived 1 passage in organ cultures of human embryo trachea, others survived 2 but not 4 passages in roller-tube cultures of human embryo kidney maintained at 33° in medium 199 When, however, this medium was supplemented with 0·2% bovine plasma-albumin and an additional 0·1% glucose, colds were produced in significant numbers by third, fourth, and eighth passage material

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SOME VIRUS ISOLATIONS FROM COMMON COLDS

II VIRUS INTERFERENCE IN TISSUE CULTURES

G HITCHCOCK
B.A Cantab

D A J TYRRELL
M.D Sheff, M.R C P

From the Common Cold Research Unit
(Medical Research Council), Salisbury, Wilts

THE first paper in this series (Tyrrell et al 1960) described experiments in which it appeared that something capable of producing colds in volunteers was being transmitted in tissue cultures of human embryo kidney cells Clearly it would be of great value to be able to recognise an infected tissue culture without recourse to inoculation of volunteers We accordingly tested in many ways cultures of the second passage of the H G P and P K. strains in human embryo kidney cultures It was not possible to stain cells specifically using the fluorescent-antibody technique No cytological abnormalities were found in cells stained by usual techniques nor when they were stained for nucleic acids with acridine orange. No excessive loss of cell proteins into the medium was detected It appeared, however, that when cultures supposedly infected with one of these viruses were inoculated with a second virus, less of the second virus was produced than in control cultures This finding was used to develop the improved methods of cultivation mentioned in the latter part of the preceding paper

Methods

Cultures

Human embryo kidney cultures prepared as described by Tyrrell et al. (1960) were used throughout, unless otherwise stated Medium 199 was used for maintenance and cultures were incubated at 33°C with rolling

"*Cold viruses*" were those described previously

Challenge Viruses

The Sendai strain of parainfluenza virus type 1 (Andrewes et al 1959) was used as infected allantoic fluid The usual inoculum was about 0·2 hæmagglutinating (H.A.) unit per culture

The U strain of Echo 11 virus (Philipson and Rosen 1959) was used as a pool of tissue-culture fluid. The usual inoculum was about 0·2 H.A. units or 1000 ID_{50} per culture.

Hæmagglutination was usually measured using 1% human red cells in phosphate-buffered saline at room temperature

Demonstration of Interference

Groups of 5–10 tissue cultures were inoculated with virus or control material. 5 days later all or half the medium was removed and challenge virus was added in fresh medium. Incubation was continued for 2 or 3 days and on one or both of these days the hæmagglutinin titre of the medium of each culture was determined The geometric means of these titres were calculated for each group A difference of 2 on $\log_2$ scale was regarded as significant on the basis of the statistical analysis of

TABLE I—EXAMPLE OF AN INTERFERENCE EFFECT IN CULTURES CHALLENGED WITH ECHO 11 VIRUS 5 DAYS AFTER RECEIVING COMMON COLD WASHINGS

Inoculum	H.A. titres of individual tubes	$\log_2$ geometric mean H.A. titre	Interference index (by difference)
Washings of patient with cold 2 days after onset	6, 2, 2, 2 0, 0, 4, 2 0 2	0·95 (a)	2·6 (c−a)
Washings of same patient without cold	12 6, 8 12, 8 8, 8, 6, 4, 2	2·7 (b)	0·85 (c−b)
0·5% bovine plasma-albumin in Hanks saline	8, 8 16 6 32, 16, 16, 16, 8 8	3·55 (c)	

some representative experiments About the same mean titres were found in cultures primarily inoculated with saline, with medium from cultures which had not received cold viruses, or with washings from volunteers without colds Cultures inoculated with material derived from subjects with colds frequently gave a significantly reduced titre, and a typical experiment is shown in table I The difference between the log of the mean hæmagglutinin titre of a test group of cultures and that of a control group was calculated and called the interference index

Results

In the first experiments, washings containing H G P virus were added to cultures and medium from these cultures was transferred to further cultures These cultures were challenged and found to show interference, which was detected on challenge at 4 or 5 days but not at 2 or 8 days Interference was demonstrated when either Sendai or Echo 11 virus was used for challenge, but the latter gave more reproducible titres and therefore more significant differences in titre The differences seemed to be of about the same magnitude whichever virus was used Other hæmagglutinating viruses were tested but seemed less satisfactory Results were best read 2 or 3 days after adding the challenge virus, later on, the difference between the infected and control cultures was often much less striking

TABLE II—INTERFERENCE IN CULTURES INOCULATED WITH HUMAN NASAL WASHINGS

Source of washing	Interference index in cultures receiving washing collected	
	During cold	After cold
Subject		
S W	*2 2*	0 4
F E B	*2 8**	−0 3
P P	−0 6	−0 1
D T	0 2	−0 3
Pooled washings from volunteers receiving		
H G P	*4 1*	0 6
D C	1 2	

* *Para-influenza-1 virus used in this experiment, Echo 11 in all others*
Significant values of the interference index are shown in italics

Washings were taken from adults suffering from colds and again after they had recovered These were tested for the presence of virus by the interference method and the results are shown in table II No interference was detected in cultures receiving material obtained from volunteers who had recovered from their colds but interference was evident in cultures inoculated with material from 2 of 4 natural colds and from 1 of 2 groups of volunteers given experimental colds No interference was apparent in cultures given second or third passage H G P virus grown without bovine plasma-albumin (B P A) and glucose supplements, a finding in agreement with the results of inoculating volunteers (cf table II of preceding paper) Interference was also observed in cultures inoculated with 2 other pools of washings obtained from different volunteers inoculated with the H G P strain and with 2 other pools from volunteers receiving the P K strain.

In an attempt to improve the sensitivity of the method the medium was supplemented with an additional 0 1% glucose and with 0 2% B P A (fraction V) during the period between inoculation of cold material and inoculation of the challenge virus Preliminary experiments suggested that both of these measures increased the amount of interference, one such experiment is shown in table III

TABLE III—EFFECT OF ADDITIONS TO MEDIUM 199 IN THE DEVELOPMENT OF INTERFERENCE IN CULTURES INOCULATED WITH FLUID, FR CULTURES INOCULATED WITH WASHINGS CONTAINING H G P VI

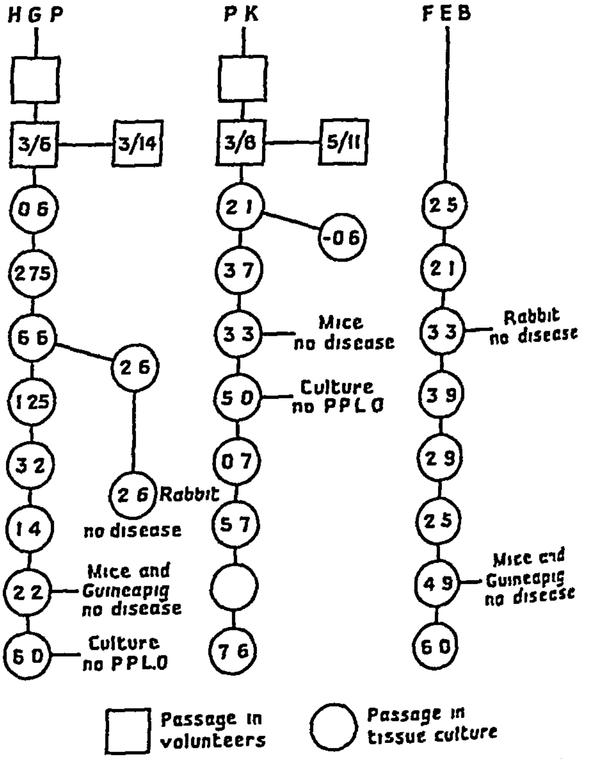
Final concentration (%) in medium of		Interference index*
Glucose	Bovine plasma albumin	
0 1	0	−0 5
0 1	0 2	2 75
0 2	0	1 25

* Challenged with Echo 11 virus

Using these supplements, attempts were made to propagate serially the factor which was apparently interfering with multiplication of the challenge virus As starting material we used the two positive specimens referred to in table II (F E B and S W) and the two strains previously studied in volunteers (H G P and P K) All but S W were successfully propagated through 8 serial tissue-culture passages without difficulty, except that 2 attempts had to be made at the second passage of P K These experiments are summarised in the figure Significant interference was observed at almost every passage It will be recalled that in the previous paper evidence was presented that fluids from the third, fourth, and eighth passages of F E B caused colds in volunteers

Considerable effort was expended in attempts to detect known viruses It was thought that viruses occurring as contaminants would turn up as readily in the control series as in the series initiated from nasal washings, yet there seems in each passage experiment a regular difference in response between each pair of the two series of cultures

No hæmagglutinin was detected though culture fluids were tested with human, chicken, ox, mouse, and guineapig cells a



Schematic representation of serial passages of material from colds Uninoculated cultures were passed serially in parallel with each of these Both were challenged and the difference in mean titres between the two groups—the interference index—is recorded for each passage The fifth control passage of F E B was contaminated Interference titres after this are given relative to H G P control cultures inoculated and challenged at the same time The numbers in the square representing a passage in volunteers give the proportion of volunteers developing colds

4°, room temperature, and 37°C, and the cell sheets were tested by hæmadsorption. The fluids were inoculated subcutaneously, intraperitoneally, and intravenously into rabbits without obvious ill effect. Similarly, guineapigs, weanling mice, and 1-day-old suckling mice were inoculated by various routes and all remained well. It was not found possible to cultivate pleuropneumonia-like organisms or other ærobic or anærobic bacteria from the tissue-culture fluids. No interference was detected in cultures of calf kidney, human thyroid, or rhesus kidney cells inoculated with material which produced interference in cultures of human embryo kidney.

Properties of the Interfering Agent

The preceding experiments seemed to indicate that a self-propagating factor had caused the interference and that it had probably originated in the washings. We therefore attempted to find out whether its properties resembled those of the virus which caused colds in volunteers. Experiments on this subject are summarised in table IV. Attempts were made to demonstrate neutralisation by pooled human γ-globulin. Apart from one possibly positive result these failed for technical reasons, arising from the toxicity for culture cells of the globulin used. It could nevertheless be concluded that the interfering factor was ether-stable, filtrable, and destroyed by heat (56°C for 30 minutes), and exposure to pH 2. In these respects at least it was apparently identical with the virus producing colds. The effect of acidity and the fact that it was self-propagating distinguished it from interferon (Lindenmann, Burke, and Isaacs 1957).

TABLE IV—SOME PROPERTIES OF THE AGENT WHICH CAUSED INTERFERENCE IN THE SERIES OF EXPERIMENTS INITIATED WITH H.G.P. MATERIAL

Source material	Treatment	Interference index of	
		Treated material	Untreated material
Nasal washing	20% ether overnight	5·5	5·5
Second pass T.C.	„ „ „	5·25	4·1
Sixth pass T.C.	Heat at 56°C for 30 min.	1·3	2·2
Fourth pass T.C.	„ „ „ „ „ „	−1·2	2·6
Fourth pass T.C.	Passage through gradocol membrane A.P.D. 290 mμ	2·7	2·6
Second pass T.C.	Dialysis against citrate buffer pH 2·1 for 3 hr	−0·8	6·6

These results are discussed at the end of the third paper (Tyrrell and Parsons 1960).

Summary

Virus interference has been detected in cultures inoculated with common-cold material and not in cultures inoculated with control material. This interference was found in cultures up to eight in series, maintained in medium 199 modified by increase in the content of glucose and addition of bovine-plasma albumin.

In experiments with H.G.P. material it was found that interference did not develop when the inoculum had been heated at 56°C, or held at pH 2. It did develop when the inoculum had been treated with ether or filtered through a gradocol membrane of average pore-size 290 mμ.

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SOME VIRUS ISOLATIONS FROM COMMON COLDS

III. CYTOPATHIC EFFECTS IN TISSUE CULTURES

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WHEN trying to make the sixth tissue-culture passage of strain P.K., described in the previous paper (Hitchcock and Tyrrell 1960) we found that a new batch of medium 199 was toxic to the cultures. Several different batches of this medium were therefore obtained. These were found to be non-toxic and so an attempt was made to make another passage. In cultures maintained with one of the new batches of medium 199 a definite cytopathic effect was observed after inoculation with tissue-culture fluids thought to contain P.K. and H.G.P. viruses. A preliminary study of this unexpected observation has now been made.

All the materials and methods were as described in the previous papers with the modifications to be found below.

Results

It was thought that the cytopathic effect might have occurred because the new medium 199 contained less bicarbonate (0·09%) than those used previously (0·16%). This was confirmed when it was found that other media with a low bicarbonate concentration allowed the appearance of a cytopathic effect. The development of this effect has been observed in kidney cell cultures, mainly of rhesus monkey but also of human and cynomolgus monkey tissue maintained in a variety of media and inoculated with from one to many thousand infectious doses of virus. We give here a general description of these degenerative changes, which seem to be basically the same under all the conditions studied.

2–7 days after inoculation foci of degeneration are seen. They consist of a few cells in which the cytoplasm becomes refractile or looks like ground-glass. The cells draw away from the surrounding cells and the cytoplasm becomes irregular in outline with long branching processes and small nodules on the cell surface. Later the cells become rounded and fall off the glass. In some cases the foci remain almost unchanged for over a week. In others they gradually extend. In human kidney cultures the foci appear throughout the sheet and extend

TABLE I—CYTOPATHIC EFFECT OF H.G.P. VIRUS IN VARIOUS TYPES OF CULTURES OF KIDNEY CELLS

Species	Variations in the conditions of culture*	Average score of degeneration†	
		At 5 days	At 10 days
Rhesus	Standard Primary cultures Primary cultures 0·1% bicarbonate	1·2 1 0	2·5 1 0
Rhesus	Standard Stationary	2·5 1·1	3 1·5
Rhesus	Standard 36°C	2 0·5	3 0
Rhesus	Medium 199, 0·16% bicarbonate 36° Primary cultures	0	0
Cynomolgus	Standard	0·8	1·2
Human	Primary cultures	0·8	N.D.

*The standard conditions were the use of secondary cultures maintained at 33°C in a roller drum with a medium containing 2% calf serum and 0·25% lactalbumin hydrolysate in Hanks' saline containing 0·03% sodium bicarbonate. Deviations from these standard conditions are shown but all other conditions remained standard throughout the experiment.

†An arbitrary scoring system was used in which 0·5 represents the appearance of the first few foci of degeneration and 3 represents degeneration of all cells. Groups of 3 to 5 cultures were used.

centrifugally. In rhesus kidney cultures, the foci appear at the extreme edge of the cultures and extend first all round the edge of the cell sheet and then gradually spread in towards the middle. When progressive degeneration of the sheet occurs it only becomes complete 5–10 days after the first focus has been observed. The changes thus resemble those of a very slowly progressive cytopathic effect produced by a poliovirus. Typical cytopathic changes as seen in unfixed and in fixed material are shown in figs 1–3.

Table I summarises the results of some typical experiments in which the effect of H.G.P. material from the fifth pass in human embryo kidney cultures was studied in various types of cultures maintained in various media. The inoculum was equivalent to 100 tissue-culture infectious doses under standard conditions of culture. The extent of the cytopathic effect was increased by using secondary rather than primary monkey kidney cultures, and by waiting up to 10 days, by using 0.03% bicarbonate rather than 0.1%, 33°C rather than 36°C, and in rolled rather than stationary cultures. Varying the lactalbumin hydrolysate concentration between 0.25% and 1% and the serum concentration between 0 and 4% did not prevent the cytopathic effect but there was at times some inhibition at the higher concentrations. If no bicarbonate was added, cultures became very granular and there was no cytopathic effect due to virus.

Fig 1—Secondary cultures of rhesus-monkey kidney cells maintained at 33°C in 2% calf serum, 0.25% lactalbumin hydrolysate with 0.03% bicarbonate and inoculated 8 days previously with 200 T.C.D.$_{50}$ of H.G.P. virus passed 5 times in human embryo kidney cultures. Some spindle-shaped cells can be seen but many are rounded up and degenerate. (Hæmatoxylin and eosin × 175.)

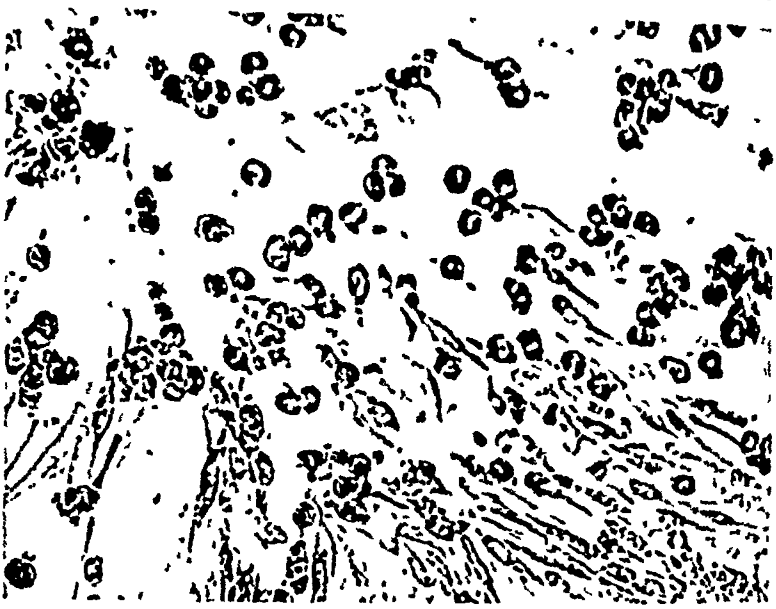

Fig 2—Similar to fig 1 but unstained (× 175).

We have formed the opinion that the exact way in which secondary monkey kidney cultures are set up and treated affects the development of cytopathic effect. We now inoculate tubes with 0.5 ml. of growth medium (Tyrrell et al. 1960) containing about 30,000 cells obtained from bottle cultures. The cultures are changed and inoculated about 2 days later when they each contain about 20,000 cells. The cells are in patches rather than continuous sheets at this stage and the pH of the medium is about 7. The cell-count rises to about 30,000 per tube and the pH falls to about 6.5 in the controls by the end of an experiment. Where there is a marked cytopathic effect the pH may be 7 or higher. In other experiments it was found that there was a slight and transitory cytopathic effect in cultures of human

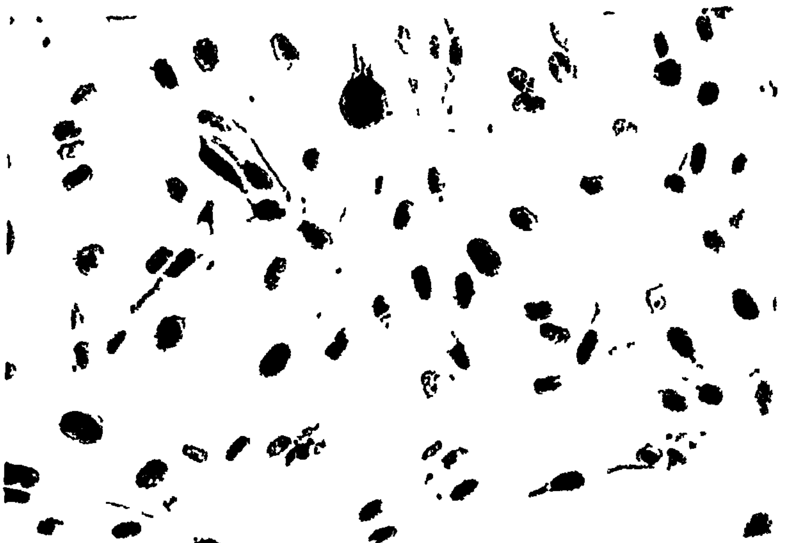

Fig 3—A parallel culture to that of fig 1 but not inoculated with virus. No degeneration. (H. & E. × 175.)

TABLE II—THE RELATION BETWEEN THE CYTOPATHIC EFFECT PRODUCED BY H.G P VIRUS AND THE INTERFERENCE EFFECT IN HUMAN EMBRYO KIDNEY CELLS

Type of culture *	State of cultures		
	Before challenge	After challenge †	
		Appearance	Log₂ Mean HA titre of challenge virus
Human kidney+H G.P	Partly degenerate	Partly or completely degenerate	1 9
„ „ —control inoculum	No degeneration	Complete degeneration	6·4
Rhesus kidney—H G.P	Partly degenerate	Complete degeneration	4 0
„ „ —control inoculum	No degeneration	Complete degeneration	2 1

* All maintained in medium containing 2% calf serum, 0 25% lactalbumin hydrolysate, and 0·03% sodium bicarbonate.
† On fifth day after inoculation with H G.P the cultures were challenged with Echo 11

embryo lung maintained at 33°C in 2% calf serum, 0 25% lactalbumin hydrolysate with 0 03% bicarbonate in the saline There was no effect in cultures of human thyroid or calf kidney cells maintained under these conditions

The cytopathic effect has been seen in over 300 cultures of human and rhesus monkey kidney cells inoculated with first to eighth passage material from strains H G P and P K With the F.E B strain, however, cytopathic effect was seen in human embryo kidney cultures but not after inoculation into monkey kidney cultures Cytopathic effect was seen in 18 of 19 human or rhesus kidney cultures inoculated with the washings containing H G P and P K which were used to initiate the serial cultures mentioned earlier No effect was seen when the washings were inoculated into cynomolgus kidney cultures The agent causing this effect has been readily passed in series The effect has never been seen in over 100 cultures receiving control material, either fluids from cultures of the uninoculated passage series or washings from several volunteers without colds

This cytopathic effect was compared with the interference effect observed previously As table II shows, human embryo kidney cultures which showed a cytopathic effect were resistant to reinfection with Echo 11 virus while corresponding rhesus kidney cultures were not This was in line with previous findings

Dr M S Pereira of the Virus Reference Laboratory, Colindale, and Dr D Hobson of the Virus Research Laboratory, Lodgemoor Hospital, Sheffield, kindly allow us to state that in "blindfold" experiments they have detected cytopathic effects in cultures inoculated with H G P and P K strains and none in cultures inoculated with control material

Properties of the Cytopathic Agents

The cytopathic effect was not prevented by treating the inoculum with ether but it was destroyed by heating at 56 C for 30 minutes and by treatment at pH 2 The cytopathic agent also passed a gradocol membrane of APD 100 mμ The H G P agent was not destroyed by blending culture medium for 2 minutes at room temperature with 4 volumes of fluorocarbon (Arcton 63) and centrifuging lightly These experiments were done quantitatively (table III) The infectivity titrations were carried out as with other cytopathic viruses serial dilutions of virus were inoculated into groups of cultures and the final reading was taken 10–14 days after inoculation Preliminary attempts were made to identify the H G P virus by neutralisation tests using tissue cultures of rhesus or human kidney cells 100 TCD_{50} were held at 37°C for 4 hours with serum before inoculation Cultures were observed for the appearance of specific degeneration The virus was not neutralised by antisera neutralising Echo 28 (the J H and 2060 viruses) and the Coe virus, both of which produce a similar degeneration, have similar physical properties, and are associated with minor respiratory infections (Andrewes 1959) It was not neutralised by hyperimmune typing sera against poliovirus types 1–3, Coxsackie B viruses types 1–5,* nor by pooled sera against Echo viruses types 1–3 and 5–14 †

TABLE III—PROPERTIES OF POOLS OF VIRUSES H G P AND P K PROPAGATED IN TISSUE CULTURE

Treatment	Titre (T C.D $_{50}$ per ml) of pool of	
	H G P	P K
Overnight with 20% ether	$10^{1\,3}$	$10>^{4\,6}$
Heated 56 C 30 min	0	0
Exposure to pH 2 1 buffer	0	0
Untreated control	10^{3}	$10>^{4\,6}$
Blending with Arcton 63 2 min and centrifugation	$10^{2\,5}$	N D
Untreated control	$10^{3\,2}$	N.D
Filtration through collodion membrane of APD 290 mμ	$10^{1\,5}$	$10^{\,3}$
100 mμ	$10^{1\,3}$	$10^{\,5}$
69 mμ	0	0
Not filtered	N.D	$10^{2\,5}$

0 = titre of less than $10^{1\,5}$ per ml N D = not done.

TABLE IV—SUMMARY OF RESULTS OF EXPERIMENTS WITH THE H G P AGENT

—	Result of experiments detecting agent by			
	Colds in volunteers	Interference	Cytopathic effect	
Conditions of culture	*Transmitted*	*Transmitted and or demonstrated*	*Transmitted*	*Demonstrated*
Medium 199	2 passages	2 passages	2 passages	—*
Medium 199—BPA and glucose	8 „ (?)	8 „	8 „	—
Human embryo kidney 33 C	—	—	—	—*
36 C	—	—	N D	—
Human embryo lung 33 C	—	—	N D	—
Human thyroid 33 C	—	—	N D	—
Rhesus kidney 33°C	—	—	—	—*
Properties of agent				
Heat at 56 C for 30 min	N.D	Destroyed	Destroyed	
Ether treatment	Stable	Stable	Stable	
Treatment at pH 2	Destroyed (?)	Destroyed	Destroyed	
Filtration membrane 290 mμ	N.D	Filtered	Filtered	

* Positive when low bicarbonate medium was used. N.D = Not done.

Neutralisation tests were performed with sera which had been collected from subject H G P at the onset and after the cold during which the washing yielding the H G P strain was taken the first serum had a titre of less than 5 and the second of 20

Discussion

The finding that some viruses from common colds will grow and produce cytopathic effects in cultures has been reached by following a series of clues First, as recorded in the first paper of this series, was the evidence of survival and probable limited growth of a pathogenic agent in tissue cultures of human embryo kidney, tentative conclusions were reached as to what were the best conditions, particularly in regard to the advantages of cultivation at 33°C Next, the discovery of some interference with growth of other viruses under these conditions of culture permitted experiments less cumbersome than inoculation of volunteers Thus were discovered modifications of medium leading to more striking results in interference tests and, soon afterwards, to evidence of propagation in series of agents producing colds in volunteers Finally as an outcome of trouble with 199 medium, it became clear that, in a more acid medium, the virus would produce cytopathic effects in cultures of human embryonic and even rhesus kidney The summary in table IV shows very good agreement between the results obtained by inoculating volunteers and by looking for interference and for cytopathic effects in cultures It is, however, worth noting that in rhesus kidney culture, cytopathic effects were seen though interference was not demonstrable It seems probable that we have cultivated the causative viruses from three cases of the common-cold syndrome This has been made possible by using human embryonic kidney, and, for some strains, rhesus kidney cultures, and maintaining these at 33°C in an acid medium These viruses grow poorly if at all under conditions more commonly used for virus cultivation It is of interest that these cooler and more acid conditions are like those which obtain at the surface of the nasal mucous membrane we also wonder whether the improved results obtained on adding B P A and glucose to medium 199 were not largely due to lowering the pH of the medium

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*Supplied by Dr P J Wormald and prepared by the Central Public Health Laboratory Colindale
†Prepared by Microbiological Associates, Washington, D C

The H G P, P K, and F E B viruses under study may, till their significance becomes clearer, be referred to as "Salisbury strains", whether they are in fact examples of a single kind of virus we do not yet know Their right to be called common-cold viruses remains to be established Several myxo- and entero-viruses have lately been recovered from minor respiratory infections, mainly in children, and some of them will produce cold-like symptoms in volunteers We have, however, not succeeded in isolating any one of them from naturally occurring typical colds of the kind under study at Salisbury (Andrewes 1959) Very possibly these myxo- and entero-viruses are causally related only to atypical "uncommon colds" in adults, the main bulk of common colds having other causes It will be noted that the Salisbury strains resemble enteroviruses in some respects The strains now described may or may not prove to be agents responsible for the commonest kind of common cold, the main objective of thirteen years' pursuit at the Salisbury unit Much further work is needed, they must be sought in washings from colds occurring naturally at different times and places, and better means of studying them serologically must be developed We anticipate that when further nasal washings are tested, some viruses, resembling H G P and P K, will be isolated directly using rhesus kidney cells as a host, however, others may be found which, like F E B, will produce a cytopathic effect only in human embryo kidney, and others, such as D C, may fail to grow at all in these hosts

Summary

A cytopathic effect has been observed in cultures of human and monkey kidney cells inoculated with washings from volunteers with experimental colds and with tissue-culture passage material

This effect was observed best in cultures maintained at 33°C in a medium containing about 0 03% of sodium bicarbonate

The agent H G P causing this effect resembled the virus causing colds in volunteers in that it was destroyed by heat and by acid conditions but not by ether treatment It passed a gradocol membrane of average pore size 100 mμ and was neutralised by convalescent serum from the subject H G P

We wish to thank Dr J Field, Dr A T Roden, Dr J S I Niven, Dr F Bang, and Mrs B Kelly for help in certain phases of these studies, and also the volunteers whose cooperation made these experiments possible

Miss J B Macdonald, S R N, assisted in the volunteer studies Dr H E M Kay supplied the human embryo tissue The monkey kidney tissue and medium 199 were supplied by the laboratory of the Medical Research Council at Hampstead, London We wish to thank all these for their help and also all our technical staff, particularly Mrs P A Palmer

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CIRCULATION IN LOWER LIMB BEFORE AND AFTER RECONSTRUCTION OF OBSTRUCTED MAIN ARTERY

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THE treatment of localised obstructions in the main limb arteries by surgical reconstruction has now become standard practice, and provided the reconstructed artery remains patent these patients regain full use of the affected limb (Rob, Eastcott, and Owen 1956)

In a series of patients with severe intermittent claudication due to a localised obstruction in a main artery of the lower limb, we have studied the arterial circulation before and after operative treatment Such functional studies are few, and are important for a fuller understanding of the circulation in health and disease

Material and Methods

The 11 male and 1 female patients all had severe unilateral intermittent claudication, and arteriography had shown a short complete block in the iliac, femoral, or popliteal artery None had clinical evidence of ischæmic disease in the other leg, the brain, or the heart The clinical details are summarised in table I The operative details have been described by Eastcott (1953)

Exercise tolerance was determined by walking the patient over two steps, and counting the number of circuits completed before the onset of pain (Hamilton and Wilson 1952)

Blood-flow was measured by water-filled plethysmographs with a venous collecting pressure of 65 mm Hg A cuff to occlude the arterial circulation of the foot was placed distal to the calf plethysmograph whose temperature was held at 33 ± 0 5 C, and the limbs were studied consecutively Reactive hyperæmia was induced by inflating the collecting cuff to 250 mm Hg for exactly 5 minutes, at the end of this time the blood-flow was recorded by releasing this cuff to 65 mm Hg, and the measurements were repeated at 30 second intervals

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TABLE I—CLINICAL SUMMARY OF THE 12 PATIENTS

Case no	Age (yr)	Sex	Location of block	Duration of symptoms	Preoperative claudication distance	Operation	Postoperative exercise tolerance	Remarks
1	47	M	Short left popliteal	2 weeks	100 yd.	4 cm frozen homograft	Unlimited	Atheroma
2	42	M	Short lt popliteal	6 mos	80 yd	Frozen homograft	„	Thrombosed fusiform aneurysm
3	50	M	Right femoropopliteal junction	6 mos	6 min. walking	9 cm homograft	Unlimited (up to 20 miles)	
4	25	M	Short rt popliteal	2 mos	100 yd	Freeze-dried homograft	Unlimited	Cystic medial necrosis with thrombosis
5	48	M	1·5 cm. calcified occlusion of rt common iliac	10 yr Some weeks	$^1/_2$ mile A few yards	Thrombo-endarterectomy	„	Calcified atheroma
6	50	M	4 cm. lt popliteal with nearby atheroma	3 mos	Less than $^1/_4$ mile	Frozen homograft	Slight limitation, no claudication	
7	50	M	Short rt superficial femoral	Several months	300 yd	5 cm. frozen homograft	Unlimited	
8	46	M	Rt popliteal	5 yr	30 yd.	11 cm frozen homograft	„	Thrombosed saccular aneurysm
9	52	M	Lt common iliac	5 yr	300 yd	Thrombo-endarterectomy	„	
10	53	M	Lt popliteal	5 mos	5 min walking	Frozen homograft	„	
11	61	M	Middle third of lt femoral	1 mo	20 yd	Autogenous 12 cm. vein graft	„	
12	44	F	Short lt popliteal	2 yr	100 yd	6 cm frozen homograft	„	

thereafter for 5 minutes by reinflating the cuff to this pressure. Blood-flow was measured simultaneously in both feet with plethysmograph temperatures ranging from 30 to 45 C, but not varying by more than ± 1°C in any one experiment. The subject was heated by immersing one or both arms in a stirred-water bath at 44–45 C, for cooling, water baths of 17–18 C were used, and, in some patients, ice was applied to the chest, and the room temperature lowered, with this exception, room temperature was maintained at 23–24°C All blood-flow rates are expressed as ml per 100 ml of tissue per minute, and each is a mean of at least four consecutive measurements at intervals of 30 seconds, except during reactive hyperæmia where individual rates of flow are recorded

TABLE II—EXERCISE TOLERANCE BEFORE AND AFTER OPERATION

Case no	Days	Before operation circuits	Days	After operation circuits
1	1–2	18–19	35	58–60
3	1–7	11–14	22	40
4	1	15	150	53
5	6	12–13	5	45
6	2–3	12–14	120	55
7	4	17–18	21	25
8	7	12	56	64
9	21	7	35–63	30–43
10	1–56	9–19	102–150	23–34
11	1–21	19–23	28	34–56

Results

Exercise Tolerance

Table II shows the number of circuits over the steps which the patient completed before the onset of claudication pain, where more than one test was performed, the range is shown After operation, claudication could not be provoked by the test in any patient except cases 6, 9, and 10, whose exercise tolerance was however, considerably improved and in whom arteriography showed a patent main arterial channel These results agree with the symptomatic improvement reported in a similar, but much larger, series (Rob et al 1956) and with the experience of many other workers Further occlusion of limb arteries developed subsequently in some patients, this conforms with the well-recognised natural history of atheroma After 400 reconstructive operations on arteries, followed for eighteen months or longer, Rob (1960) reports further arterial thromboses in 87

Calf Blood-flow

Before operation, the resting blood-flow through each calf was about the same, but the pattern of reactive hyperæmia in the two limbs was very different. In the symptomless limb the flow was maximal at the moment of release of the circulation, and declined rapidly in the following $1^1/_2$ minutes This is the normal response described by Lewis and Grant (1925) In the affected limb there was no detectable flow on release, and the maximal flow did not develop until $1^1/_2$ minutes later Fig 1 compares the flows (mean and 95% confidence limits) of the affected and symptomless legs of 8 patients before operation, and shows the abnormal pattern, and

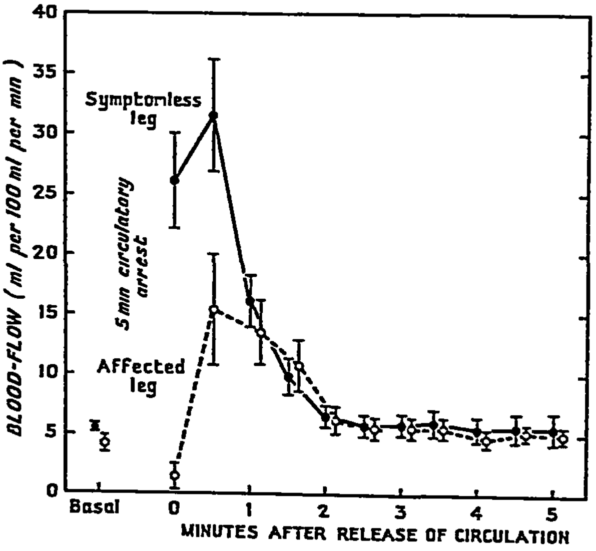

Fig 1—Calf blood-flows at rest and during reactive hyperæmia of the patients affected and symptomless limbs before operation mean and 95% confidence limits

TABLE III—BLOOD-FLOW THROUGH THE CALF (ML PER 100 ML TISSUE PER MIN) BEFORE 5 MIN ARREST OF THE CIRCULATION AND AT ½ MIN INTERVALS THEREAFTER

Group	Mean age	No of limbs	Mean resting flow	Release flow	Minutes after release of circulation									
					½	1	1½	2	2½	3	3½	4	4½	5
Old normal	64	9	6·6 ±0·48	38·1 ±4·16	36·4 ±4·39	20·7 ±4·08	13·9 ±1·77	8·9 ±0·96	8·4 ±0·60	8·0 ±0·68	7·6 ±0·70	7·4 ±0·77	7·4 ±0·69	7·3 ±0·66
Young normal	28·3	9	5·5 ±0·73	38·2 ±7·8	35·5 ±6·31	20·3 ±2·33	11·4 ±1·60	8·5 ±1·32	7·7 ±1·26	7·0 ±0·86	7·0 ±0·93	7·2 ±0·97	7·0 ±1·17	6·3 ±0·93
Patients' symptomless limb	50·6	8	5·5 ±0·86	26·0 ±4·85	31·5 ±4·73	15·9 ±2·26	9·8 ±1·54	6·5 ±0·93	5·7 ±0·92	5·8 ±0·92	5·9 ±1·17	5·4 ±0·98	5·5 ±1·24	5·5 ±1·31
Patients' affected limb Before operation		8	4·15 ±0·70	1·2 ±1·0	15·3 ±4·87	13·3 ±2·67	10·7 ±2·18	6·3 ±1·31	5·5 ±0·91	5·45 ±0·89	5·5 ±0·84	4·7 ±0·77	5·2 ±0·60	4·9 ±0·69
After operation		8	7·6 ±1·27	20·8 ±4·51	25·2 ±2·84	18·3 ±2·04	12·6 ±1·12	8·8 ±0·81	8·6 ±0·98	8·3 ±0·91	7·9 ±0·70	8·0 ±0·95	8·1 ±0·81	8·4 ±0·97

low values, of the hyperæmia flows in the diseased limbs Shepherd (1950) showed a similar slow development of maximal blood-flow in limbs with arterial insufficiency both after exercise and after circulatory arrest

For comparison with our patients, we made control studies of the calf reactive hyperæmia in 12 men who had neither symptoms nor signs of vascular disease, 6 of these were aged 20–35 and 6 were aged 55–75 Table III compares the blood-flow (mean and standard error) at rest and at half-minute intervals during reactive hyperæmia in the controls and patients before and after operation The two age-groups of the controls show very similar values, and the results have therefore been pooled for comparison with the patients in fig 2 This shows that the resting flow increases after operation, becoming greater than that in the control group, and that the hyperæmia pattern returns to normal However, the flows attained in the operated leg during the initial part of the hyperæmia are lower than those in the symptomless limbs, and these in turn are lower than in the normal limbs These relationships may reflect the integrity of the respective arterial trees, the symptomless limb being affected by clinically inapparent arterial disease, and the affected limb after operation having an arterial circulation inferior to that of its fellow, owing either to a greater amount of arterial disease or to inability of the graft to furnish a completely normal lumen The return of normal reactive hyperæmia in our patients following operation suggests that the abnormal pattern was due to the localised obstruction in the main artery, and not to disease of smaller vessels or other factors Eastcott (1953) and Gaskell (1956) found the same abnormal hyperæmia curve in patients with arterial obstruction, the pattern returned to normal when the obstruction was relieved surgically, but it reverted if the artery was occluded by further thrombosis (Gaskell 1956)

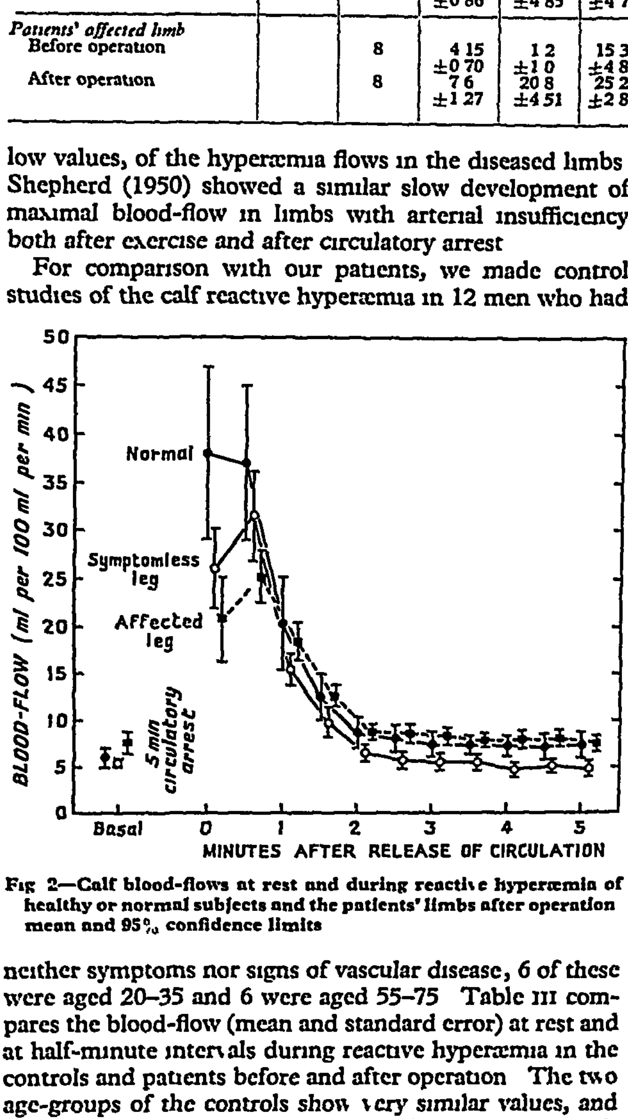

Fig 2—Calf blood-flows at rest and during reactive hyperæmia of healthy or normal subjects and the patients' limbs after operation mean and 95% confidence limits

Reactive hyperæmia may be regarded as the "repayment" of a blood-flow "debt" incurred during the period of circulatory arrest The volume of the blood debt has been estimated by assuming that the mean basal blood-flow before arrest of the circulation would have continued unchanged during the next 10 minutes if there had been no interference Thus the blood debt is this rate of flow multiplied by 5 (the minutes of circulatory arrest), and the repayment is the area of the reactive hyperæmia curve lying above this assumed basal flow Mean values of debt and repayment and an analysis of their relationship are shown in table IV The mean percentage repayment for each group has been calculated from individual repayments expressed as a percentage of their respective debts

TABLE IV—GROUP MEANS AND STANDARD ERRORS OF THE 5-MINUTE BLOOD-FLOW DEBT, REPAYMENT, AND REPAYMENT AS PERCENTAGE OF DEBT WITH THE SIGNIFICANCE OF ITS DIFFERENCE FROM 100, AND COEFFICIENT OF CORRELATION BETWEEN DEBT AND REPAYMENT WITH ITS SIGNIFICANCE

Group	No of limbs	Debt	Repayment	% repayment of debt	Difference from 100% of percentage repayment		Correlation between debt and repayment	
					t	P	r	P
Control	18	30·3 ±2·3	38·0 ±3·8	133·7±13·9	2·43	0·05 0·02	−0·25	>0·1
Patients' symptomless limb	8	27·4 ±4·3	25·5 ±4·1	103·0±19·7	0·17	>0·1	+0·33	0·1
Patients' affected limb Before operation	8	23·1 ±3·5	16·5 ±4·2	74·4±17·6	1·45	>0·1	−0·09	0·1
After operation	8	38·2 ±6·4	23·1 ±3·5	77·0±18·7	1·23	>0·1	−0·57	0·1

The smaller repayments and percentage repayments of the patients' affected and symptomless limbs is a further expression of the lower hyperæmia curves of these groups, already noted in fig 2. Operation produced a surprisingly small increase in percentage repayment (from 74 to 77), apparently at variance with the good clinical response. The explanation of this paradox may lie in the failure of the method to distinguish between skin and muscle blood-flow. It has already been observed that the resting calf flow is increased after operation (fig 2), and it is shown later that operation is followed by up to an eightfold increase in blood-flow through the foot. This suggests that operation induces vasodilatation in the limb, mainly in the skin, and hence the blood-flow debt, calculated from the resting calf flow, is larger than that due to muscle alone. Since reactive hyperæmia is mainly due to increased blood-flow through muscle, the true percentage repayment of calf muscle after operation is probably much greater than that calculated.

If hyperæmia were regulated exactly to redress the debt, the mean percentage repayment should not differ significantly from 100. Table IV shows that the percentage repayment of the control group (133·7) differed significantly from 100 ($t = 2 \cdot 43$, $0 \cdot 02 < P < 0 \cdot 05$), but it did not do so in the remaining groups. For each group a correlation coefficient of debt and repayment has been calculated, and their values and significance are shown in table IV. There was no consistent relationship between them. Freeman (1935) suggested that reactive hyperæmia was a homœostatic mechanism with the blood debt accumulated during ischæmia nicely balanced by the hyperæmia. Our results offer no support for this theory, but suggest that the magnitude of reactive hyperæmia is mainly related to the efficiency of the arterial circulation.

Apart from the general errors of plethysmography there are some special sources of error that must be borne in mind in considering these results. It is known that the arterial blood-pressure beyond an arterial obstruction may be lower than elsewhere (Edholm et al 1951), and furthermore Patterson and Whelan (1955) have shown that, on release of the circulation after a period of arrest, the arterial blood-pressure in the normal arm may take 20 seconds or more to return to its previous level. It is therefore possible that, in some of the affected limbs studied before operation, the collecting-cuff pressure of 65 mm Hg may have obstructed the entry of blood into the limb and caused falsely low estimates of flow. To investigate this possibility some of the experiments were repeated with a lower pressure in the collecting cuff, the values were found to be the same or slightly higher, and the same abnormal pattern remained in the reactive hyperæmia curve.

Foot Blood-flow

Blood-flow through the foot was measured serially in 7 patients before and after operation (table V). As would be expected, the symptomless limb usually had the greater rate of flow, especially at the higher plethysmograph temperature, but there were exceptions (cases 2–4), the special circumstances of case 5 will be described later. Without exception, operation was followed by a temporary, and often large, increase in blood-flow through the foot of the affected limb, often exceeding that in the contralateral foot. This response to operation, which will henceforth be termed the postoperative vasodilatation, was maximal 1–5 days after operation, and declined during the next few days. The degree of postoperative vasodilatation was not related to the preoperative circulatory efficiency (judged by the exercise-tolerance test and calf and foot flows) or to any other obvious factor. It was present throughout the range of plethysmograph temperatures used, and was therefore not a response to local heat. Most of these cases had a repair of an obstructed popliteal artery, so it remains uncertain whether the site of obstruction and repair is a

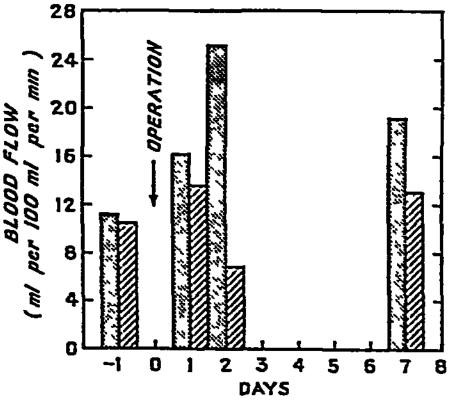

Fig 3—Case 2 foot blood-flows (plethysmograph temperature 43 C) before and after popliteal grafting. Stippled columns = operated limb. Hatched columns = symptomless limb.

TABLE V—MEAN BLOOD-FLOWS THROUGH FEET IN ML PER 100 ML PER MINUTE BEFORE AND AFTER REPAIR OF OCCLUDED MAIN ARTERIES

Case no	Site of arterial obstruction	Plethysmograph temperature (°C)	Foot	Days before and after operation: −5 or before	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10 or after
1	Lt popliteal	43	L	4·6							33·3		39·7				22·5	14·8
			R	16·5							8·0		11·9				16·6	10·5
2	Lt popliteal	43	L					11·0	16·1	25·1					18·8			
			R					10·3	13·4	6·8					13·3			
		32	L								13·8		3·6					
			R								3·7		1·1					
3	Rt popliteal	40	R	9·8					13·0		7·0		14·2			10·4		11·0
			L	19·2					12·0		7·4		7·6			18·5		9·4
		30	R				4·1			3·2	5·4			3·4		2·6		
			L				4·1			0·8	2·0			1·6		2·8		
4	Rt popliteal	33	R	3·6		3·3	5·8	4·2	21·0	11·0			5·3			6·7		
			L	3·6		3·6	5·4	4·0	4·2	2·2			3·8			2·1		
5	Rt iliac. Previous rt sympathectomy, aorta and lt iliac dissected. Rt iliac thromboendarterectomy	31	R	9·6			10·0	8·7			12·0					11·5		
			L	3·6			2·0	1·1			16·4					1·4		
		44	R		8·4			6·9			11·5						16·0	
			L		14·5			15·5			19·7						17·3	
6	Lt popliteal	44	L			8·3			18·1			15·6						9·9
			R			19·4			12·5			12·1						17·5
7	Rt femoral	44	R					5·1			7·1							9·4
			L					10·7			8·1							8·3

factor of importance in producing this phenomenon Gaskell (1956) has shown that the same phenomenon sometimes appears after repair of occluded iliac and femoral arteries, and our clinical experience agrees with this

Fig 3 shows the postoperative vasodilatation in case 2 On the 2nd postoperative day the foot blood-flow in the operated side was more than double the preoperative flow in either foot, and on the other side was less than at any other time Cases 1 and 6 showed the same reduction of blood-flow in the symptomless limb during the peak of postoperative vasodilatation

ROLE OF VASOMOTOR TONE IN POSTOPERATIVE HYPERÆMIA

To define the role of the sympathetic nerves in limbs with postoperative vasodilatation we studied the effect of heating the body This completely removes sympathetic vasoconstriction in the hand, but less completely in the foot (Pickering and Hess 1933) When applied to patients with postoperative vasodilatation, body-heating produced a rise in the blood-flow till approximately the same high level was attained in both feet (fig 4, case 2) When the body was cooled, blood-flow fell on both sides, but less on the operated side Similar results were found in further 2 patients and the response to body heating of all 3 patients is shown in table VI It will be seen that the notable difference in blood-flows through the two feet was largely abolished by heating the body

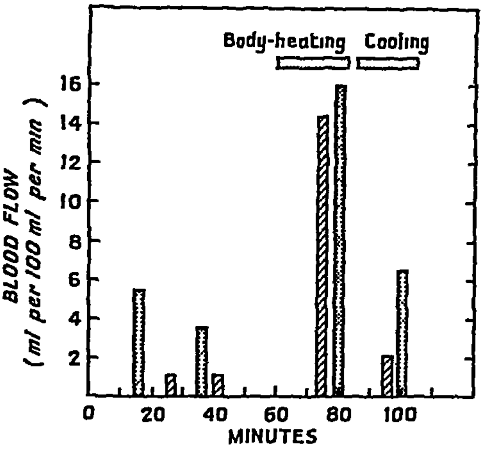

Fig 4—Case 2 effect of body heating and cooling on foot blood-flows 5 days after operation Plethysmograph temperature 32 C Stippled columns = operated limb Hatched columns = symptomless limb

These experiments demonstrate that the sympathetic nerves are still capable of altering vascular tone in the foot during the phase of postoperative vasodilatation, and that when sympathetic tone is released the vascular beds in the two feet are of similar size Hyperæmia due to a chemical vasodilator stimulus or to an enlarged vascular bed would both be expected to maintain a greater blood-flow in the affected limb even upon release of sympathetic tone Our observations on the postoperative vasodilatation are fully consistent with its being due to partial release of sympathetic constrictor tone

NATURE OF OPERATIVE STIMULUS PRODUCING VASODILATATION

Table V shows that in case 5 profound postoperative hyperæmia developed in the unaffected limb, thus the features of this case are of special interest

TABLE VI—MEAN BLOOD-FLOWS THROUGH THE AFFECTED (A) AND SYMPTOMLESS (S) FEET AFTER POPLITEAL ARTERIAL GRAFTING FLOW IN ML PER 100 ML PER MIN BEFORE AND AFTER HEATING THE FEET

Case no	Days after operation	Plethysmograph temperature (C)	Foot	Before heating	After heating
2	5	32	A	3 6	15 9
			S	1 1	14 5
	7	43	A	18 8	[illegible]
			S	13 3	[illegible]
3	2	30	A	3 2	3 4
			S	0 8	3 0
4	1	33	A	21·0	29 4
			S	4 2	23 [illegible]
	5	33	A	5 3	21 7
			S	3 9	17·0

This patient had a block about ³/₄ in long in the right common iliac artery, and 6 weeks before our studies a right lumbar sympathectomy had been performed elsewhere We confirmed that the right foot remained devoid of vasomotor innervation by observing that the blood-flow through this foot did not change with vigorous body heating and cooling At operation the aortic bifurcation and both common iliac arteries were mobilised by dissecting off the densely adherent periarterial tissues Controlling clamps were placed on the aorta and both common iliac arteries, and then the calcareous mass obstructing the right common iliac artery was extracted from it The incision in the artery was then closed

Fig 5 shows the foot blood-flow in this patient before and after operation, using plethysmograph temperatures of 44 and 31°C Before operation the affected side had the greater flow when the plethysmograph temperature was 31 C (owing to the previous sympathectomy), but this side had the lesser flow when the plethysmograph was 44 C (owing to the obstruction in its main artery) On the 1st postoperative day both pulses had returned in the right foot, but it was the left foot that was red and hot, being appreciably warmer than the right This difference in temperature persisted until the 7th postoperative day when once again the right foot was warmer than the left, as had been the case before operation Blood-flow measure-

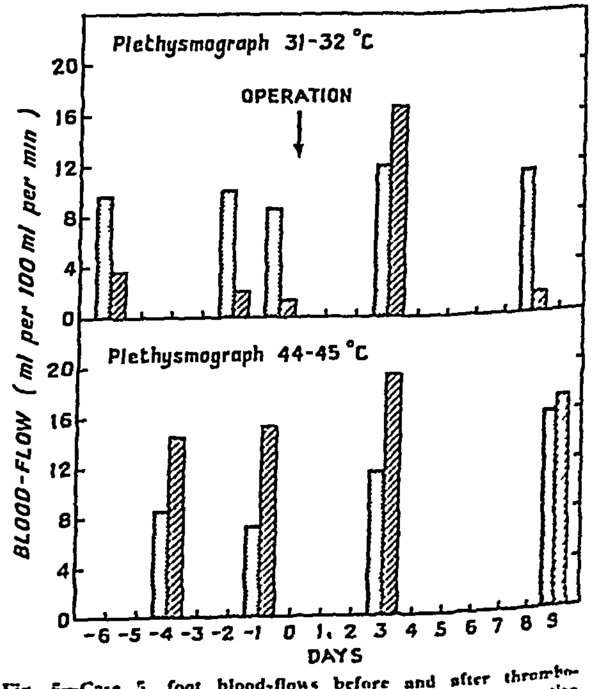

Fig 5—Case 5 foot blood-flows before and after thrombo-endarterectomy of the right common iliac artery The operation included dissecting and clamping the left common iliac artery There had been a previous right lumbar sympathectomy Stippled columns right foot Hatched columns – left foot

ments (fig 5) confirmed that the left (unaffected) limb had experienced an appreciable postoperative vasodilatation which had subsided by the 8th postoperative day, whilst there was no evidence of vasodilatation of this kind on the affected side The vasodilatation must have been related to the operative interference upon the aorta and left common iliac artery, for this patient had no more than the usual rise of body temperature of 1–2°F after operation. The vasodilatation in the left foot was similar in kind, degree, and duration to that seen in other cases on the grafted side, and suggests a similar mechanism On the 8th postoperative day the blood-flow through the left foot increased in response to body-heating from 1 3 to 8 8 ml per 100 ml per min., demonstrating that the operation had not destroyed the sympathetic nerves supplying the left leg

The only factor common to the interference with this normal limb and the reconstructive operations of other patients was the handling and dissection of the main artery This suggests the possibility that postoperative vasodilatation is due to injury of the artery or destruction of the periarterial plexus of nerves The latter mechanism seems more likely in view of the other evidence suggesting that the response was mediated by a partial release of sympathetic vasomotor tone

Discussion

Striking changes followed reconstruction of the main artery in these patients One or both of the foot pulses returned during the operation or shortly afterwards, and the foot became hot and red, often for several days The blood-flow through the resting calf as well as through the foot was greater in the operated than in the contralateral limb for many days after operation

Calf Blood-flow

Intermittent claudication was largely, or completely, relieved by operation and the reactive hyperæmia returned towards the normal pattern The reversal of these abnormalities after operation suggests that in the main they resulted from a single obstruction in a main artery

The slight impairment of reactive-hyperæmia flows in the calves of both operated and symptomless limbs is probably due to further, lesser, arterial obstructions, such measurements are of value in the study of groups of patients, but the overlap with the normal deprives them of individual diagnostic significance

The response of blood-flow to ischæmia was termed reactive hyperæmia by Lewis and Grant (1925), who considered that it was occasioned by the accumulation of metabolites Further, in 1938 Grant showed that the hyperæmia following exercise was governed by the amount of exercise undertaken, and that it was independent of the sympathetic nerves Freeman (1935) claimed that a self-regulating system must be responsible for the approximate correlation which he demonstrated between the blood debt incurred during circulatory arrest and the subsequent excess flow It has been found that the excess blood-flow of reactive hyperæmia and after exercise is independent of the resting flow whether this has been elevated by heating the body (Barcroft et al 1952) or reduced by infusing adrenaline (Dornhorst and Whelan 1953) Similarly the excess flow is no greater when the effective local blood-pressure is reduced, or when arterial hypoxia is induced (Dornhorst and Whelan 1953) It was therefore postulated by Barcroft and his colleagues (1952) that two functionally independent types of vessels existed in muscle one responding to metabolites and the other under the control of the sympathetic nerves Dornhorst and Whelan (1953), however, considered that these findings were adequately explained by assuming that the removal or destruction of metabolites depended on a concentration gradient from tissues to the vessels, and not on the level of blood-flow or oxygen tension Patterson and Whelan (1955) found, like us, a poor correlation between blood debt and repayment, and a percentage repayment ranging from 50 to 200 Duff et al (1955) observed the effect of antihistamine drugs on reactive hyperæmia and found evidence for the accumulation of histamine only when the circulation had been arrested for 10 minutes or longer There is evidence that the transmural pressure of arteries may partly govern their calibre (Bayliss 1902), Folkow 1949, Greenfield and Patterson 1954), and that this mechanism may play a part in reactive hyperæmia (Patterson 1956)

Thus many factors may be responsible for reactive hyperæmia, and in these circumstances it is perhaps not surprising that there should be only an approximate relation between blood-flow debt and repayment In our subjects the repayment reflected the integrity of the arterial circulation, being greatest in the normal group, intermediate in the patient's symptomless leg, and least in their affected leg Furthermore those patients with the greatest circulatory impairment had the smallest repayments

We infer from these results that, in the healthy subject, the excess blood-flow during reactive hyperæmia is not regulated exactly to balance the debt incurred by ischæmia By the action of multiple factors this hyperæmia may be normally well in excess of homœostatic requirements and its extent largely a reflection of the integrity of the arteries

Foot Blood-flow

The major point of interest resulting from the studies on foot blood-flow is its temporary, and often large, increase following repair of the main artery, a similar temporary increase in foot blood-flow following arterial grafting was reported by Eastcott (1953) and by Gaskell (1956), who concluded that restoration of the arterial pathway—and not any other aspect of the operation—was the cause of the hyperæmia There is much evidence from our own and other studies that the arterial vessels of an ischæmic limb may be dilated, and it might be supposed that the increased flow after operation is simply due to a higher pressure within persistently dilated vessels However, as both our and Gaskell's studies show, in the ischæmic limb the vessels are more dilated in muscle than in skin, whereas the postoperative increase of flow is much more prominent in skin than in muscle In addition we have produced a similar hyperæmia in a normal limb where the only interference was dissection of the periarterial tissues Although we cannot yet identify with certainty the cause of the postoperative vasodilatation, our data suggest the tentative hypothesis that the phenomenon is due to a partial release of sympathetic vasomotor tone, caused by the destruction of the periarterial nervous plexus at operation

The effect of destroying the periarterial sympathetic nerves on the blood-flow in the limb has long been disputed, and physiological aspects have been lost sight of amid the conflicting therapeutic claims

Perivascular denervation was first suggested by Jaboulay (1899) and was later strongly advocated as a treatment for ischæmic disease by Leriche (1921) Leriche found that denuding the artery of its sheath over a length of 8 to 10 cm caused contraction of the artery, with loss of its pulse, and a fall of the skin temperature of the operated limb lasting 3–15 hours The pulse then reappeared and the limb became noticeably warmer, its temperature exceeding that of the unoperated side by 2–3 C This vasodilatation was transitory, however, waning 5-6 days later, and vanishing within 3–4 weeks Brown and Rowntree (1925) measured the heat elimination from the hand in a patient with Raynaud's disease before and after periarterial sympathectomy After operation, the elimination increased to a maximum in 5–8 days and returned to its pre-operative level in 2 weeks In a patient with Buerger's disease, these workers found no changes in heat elimination from the hand after periarterial sympathectomy Rogers and Hemingway (1930) studied the problem in cats The change of the hindlimb volume to histamine and acetylcholine injections was measured before and after destruction of the periarterial nerves Soon after operation, vasodilatation could be shown by this method, though evidence of it had disappeared by the end of the experiment They obtained more direct evidence of vasodilatation by observing the vessels of the rabbit's ear, after destruction of the periarterial nerves of the carotid artery, the ear remained redder and warmer than the other side for 48 hours Woollard and Phillips (1932) measured the skin temperature of their own hands before and after injecting procaine around the radial and ulnar arteries With this method they were unable to detect any changes, but there was no reliable evidence of paralysis of the periarterial nerves Other published work on periarterial sympathectomy deals solely with the clinical appraisal of its sequelæ However, the time relationships of the clinical improvement in the circulation and its subsequent relapse followed, in many cases, the pattern described by Leriche

The postoperative hyperæmia exhibited by our patients is therefore similar in degree and duration to the changes recorded by previous workers after division of the periarterial nerves We therefore consider that division of periarterial nerves is the likeliest main cause of the postoperative vasodilatation here described

Summary

In 12 patients with a localised obstruction of the iliac, femoral, or popliteal artery, the arterial circulation was investigated by plethysmography before and after reconstructive operations The obstruction was relieved by an arterial homograft in 9, by an autogenous vein graft in 1, and by thromboendarterectomy in 2

After operation intermittent claudication was greatly relieved or abolished

Blood-flow through the calf was measured at rest, and during reactive hyperæmia, in 8 patients and in a control group of 12 healthy men In the affected limb, resting calf flow was sometimes equal to, or even greater than, that in the contralateral limb, but the calf reactive-hyperæmia curve had an abnormal form, and was lower than in the other limb The normal calf reactive hyperæmia was greater than that in the patients' symptomless limbs In the early postoperative period, the affected limb had the larger resting flow, and its reactive-hyperæmia curve became higher and assumed a normal shape

The percentage " repayment " by reactive hyperæmia of a calf blood-flow " debt " incurred by 5 minutes' circulatory arrest averaged 134 in the normal group, 103 in the patients' symptomless limb, and 74 in the affected limb These findings suggest that reactive hyperæmia is not a nicely balanced response, but a vasodilatation induced by many independent causes with the integrity of the arteries as a limiting factor

Foot blood-flow was measured serially in 7 patients Preoperatively it was usually, but not invariably, reduced on the affected side After operation the foot flow in the operated limb increased in all patients, in 5 of them exceeding the flow in the other foot for several days Evidence is adduced that this postoperative vasodilatation is due to partial release of sympathetic tone induced by interruption of the periarterial plexus of nerves

These studies were suggested by Sir George Pickering, to whom we are grateful for encouragement Our thanks are also due to Prof C G Rob for allowing us to study his patients

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TECHNIQUE OF IRRADIATION OF CONSCIOUS PATIENTS UNDER INCREASED OXYGEN PRESSURE

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IT has been known for many years that plant cells are more susceptible to damage when irradiated under aerobic than under anaerobic conditions, and in experiments with the roots of *Vicia faba* Thoday and Read (1947) showed that, as the oxygen tension rises from zero, the radiosensitivity also increases—steeply at first but more slowly later In 1953 Gray et al established that in mice the sensitivity of the Ehrlich ascites tumour is raised by high oxygen tension Clinically, Churchill-Davidson et al (1955, 1957) demonstrated the enhanced effect of radiation on patients breathing oxygen at *3 atmospheres pressure*, and reported some promising results with the method

This treatment under oxygen at high pressure involved the use of a metal pressure chamber, general anæsthesia to enable patients to tolerate the chamber, and bilateral myringotomy to prevent damage to the middle ears As ill patients could not have repeated anæsthesia, two large treatments only were given, and, because of the time taken to anæsthetise and prepare the patients, only a few could be treated The normal method of irradiation by fractionation daily for a number of weeks could not be applied, and the treatment could not be used as a routine for large numbers of patients A further disadvantage was that the anæsthesia might well decrease the sensitivity of the tumour cells, thus partially counteracting the beneficial effects of the high-pressure oxygen (Burdick 1953)

In an attempt to obviate these disadvantages, we decided to investigate the possibility of treating large numbers of conscious patients under high oxygen tension with the usual fractionation techniques For this purpose we

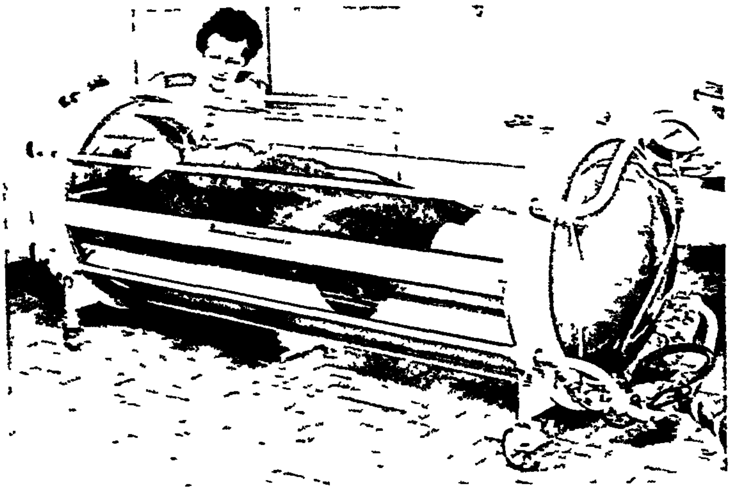

Fig 1—Complete chamber

needed a pressure chamber which would be acceptable to the average conscious patient, and would be applicable to routine radiotherapy techniques, without shortening the time in which the machines were in use The special problems posed by these requirements were

1 Production of a mobile chamber, able to withstand at least 1 atmosphere above ambient, which would allow continuous visual and auditory contact with the patient.

2 Elimination of any features which would make the conscious patient unwilling to undergo this form of treatment.

3 Elimination of the risk of an explosive decompression, which might endanger bystanders and affect the patient because of the sudden drop in pressure.

4 Development of a system of pressurisation which would at least minimise ear and sinus pain or damage (otitic sinus barotrauma) These syndromes are caused by difference of pressure between the environment and the sinus and middle-ear cavities

5 Provision of adequate ventilation, to give full oxygenation and to prevent retention of water vapour and carbon dioxide inside the chamber

The Chamber

A transparent chamber, pressurised through an electromechanical automatic control system, was designed and constructed (fig 1) It is a 'Perspex' cylinder (6 feet long and 26 inches in internal diameter) mounted on wheels Its ends are fibre-glass domes supported in aluminium rings One end dome is removable and is used for entrance of the patient, who lies on a movable bed (fig 2) In an emergency the chamber can be depressurised from 1 atmosphere above ambient within half a minute To remove the risk of an explosive decompression the perspex cylinder is made as a double skin whose interlayer is partially filled with glycerin This distributes the stresses between the two parts of the structure. and in the remote possibility of the inner skin failing, the pressure would be retained by the outer skin

All the control gear is mounted on a small panel remote from the chamber and connected to it by a flexible hose 100 feet long The flow of oxygen from cylinders to the chamber can be varied, in practice a flow of approximately 5 cubic feet per minute has been found satisfactory This gives good pressurisation rapidly sweeps residual air out of the chamber (which has a volume of about 20 c ft.) provides a comfortable environment for the patient and prevents the build-up of water vapour and carbon dioxide. The pressure inside the chamber is controlled by a motorised spring-loaded valve on the outlet side This valve, when set, gives a constant rate of pressure change, this setting can be varied from 1 to 2 lb per sq in per minute by adjusting the speed of rotation of the motor The layout of the control system, is shown in fig 3 An intercommunication system is incorporated in the apparatus so that the patient, the operator of the chamber, and the radiographer giving the treatment, can be in constant communication with each other

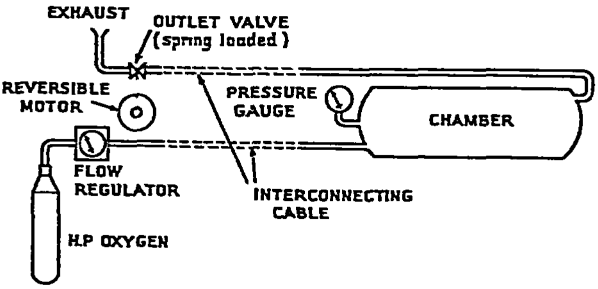

Fig 3—Layout of the chamber pressurisation system

Experience of the Method

This chamber has been employed since January, 1959, for the treatment of patients with carcinoma of the bronchus by the techniques in use in the radiotherapy department at University College Hospital (Hilton and Pilcher 1955) These entail daily treatment for from four to seven weeks The patients have withstood their radiotherapy well and the transparency and ease of communication have enabled them to enter the chamber with confidence. As in normal techniques the irradiation is applied under visual control and the patient can be observed throughout The mobility and small size of the chamber make possible its use with the standard radiotherapy units The total time from entering the chamber to the end of depressurisation is usually under half an hour and as pressur-

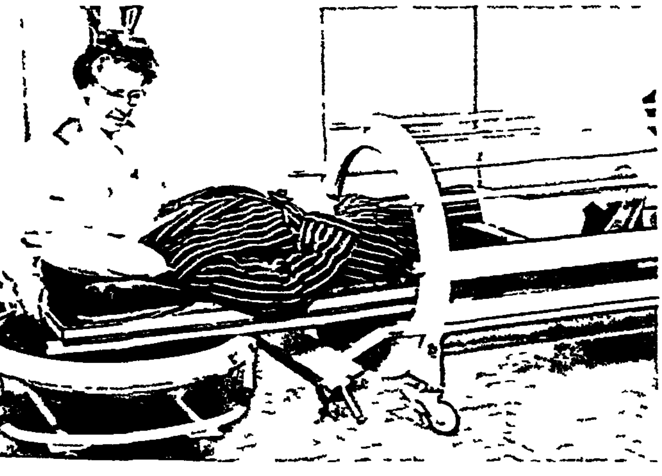

Fig 2—Method of entry of the patient.

isation and depressurisation take place outside the treatment room, the radiotherapy machine can be in continuous use The whole technique is simple and has not necessitated any increase in staff It should be noted that although the rate of pressure change used is normally 2 lb per sq in per minute, there has been no pain or damage in ear or sinus This may possibly be attributed to the smooth pressurisation attained by the automatic control system

In view of the success of this chamber, we hope to develop the technique so that it can be used for treating conscious patients at pressures up to 4 atmospheres absolute

We are grateful to Dr Gwen Hilton, director of the radiotherapy department, University College Hospital, and to Dr C F Bareford, managing director, Vickers Research Ltd , for their invaluable help and encouragement in this project

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INVESTIGATION OF HYPERPARATHYROIDISM IN THE ABSENCE OF BONE DISEASE

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MANY patients with hyperparathyroidism present with renal calculi and not with the classical features of bone disease, hyperphosphatasia, hypercalcæmia, hypophosphatæmia, and hypercalciuria, in some of them disturbances of serum-calcium or plasma-phosphorus are absent

Because of the known effect of parathyroid hormone on the renal tubules (see, for example, Hiatt and Thompson 1957) many investigators have studied the renal handling of phosphate in hyperparathyroidism Phosphate-clearance (Kyle, Schaaf, and Canary 1958), and the ratio of phosphate-clearance to creatinine-clearance (C_i/C_{cr}) (McGeown 1957), have been investigated extensively, a phosphate-excretion index (P E I) (Nordin and Fraser 1956) and percentage tubular reabsorption of phosphate ("%T R P) (Goldman, Gordan, and Chambers 1957, Thomas, Connor, and Morgan 1958) have been derived from the clearance ratio But none of these indices of phosphate disturbance have given an unequivocal distinction between patients with hyperparathyroidism and those with renal calculi associated with other conditions

We have used a technique described by Anderson (1955a) to study the theoretical renal phosphorus threshold in proven cases of hyperparathyroidism, and in other patients with no evidence of parathyroid overactivity So far a clear distinction has emerged between patients with hyperparathyroidism and those with idiopathic renal calculi

Patients Studied

GROUP 1 *Hyperparathyroidism* (Cases 1–7)

Seven patients had hyperparathyroidism proven by surgical removal and histological examination of adenomata. Six presented with renal calculi and one had malignant hypertension without renal calculi or nephrocalcinosis None had biochemical or radiological evidence of bone disease

GROUP 2 *Renal calculi* (Cases 8–17)

Ten patients with calcareous renal calculi were comparable in age and range of renal function with those of group 1 These patients were not considered to have hyperparathyroidism and therefore none was explored for parathyroid lesions

GROUP 3 *Idiopathic hypercalciuria* (Cases 18–20)

Three patients had idiopathic hypercalciuria Case 18 had had multiple renal calculi for 9 years Case 19 had nephrocalcinosis Case 20 had had recurrent renal calculi for 20 years, and exploration of the neck in October, 1957, revealed normal parathyroid glands

GROUP 4 *Others* (Cases 21–28)

Two patients had idiopathic phosphaturia, in one it was associated with renal glycosuria, and in the other with amino-aciduria Three were normal hospital patients Two were cases of acromegaly One was a case of steatorrhœa with osteomalacia

Methods

Measurement of Renal Phosphorus Threshold

Outline of procedure—A linear rise in plasma-phosphorus of about 8 mg per 100 ml was produced by an intravenous infusion of buffered sodium phosphate over a period of 180 minutes Urine was collected at 30-minute intervals, and blood was taken at the mid-point of each urine-collection period The inorganic phosphorus in each blood and urine sample was estimated (In this paper "plasma-phosphorus" refers to the plasma-inorganic-phosphorus level) Plasma phosphorus was then plotted against time to confirm that a linear rise had occurred, and the plasma phosphorus at the mid-point of each urine collection period was obtained by interpolation The theoretical renal phosphorus threshold was calculated from a second graph with the urinary phosphorus excretion (mg per min) in each period as ordinate and the corresponding plasma phosphorus as abscissa The regression line was calculated The plasma pho-

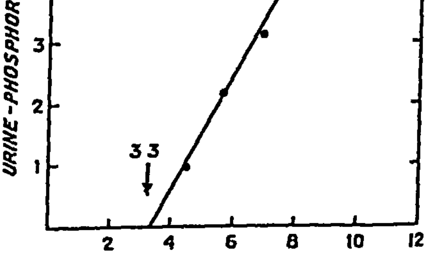

Fig 1—An example of the determination of the theoretical renal phosphorus threshold (case 15)

The six points represent the plasma-phosphorus levels and urinary output of phosphorus during six periods of infusion The regression line was calculated (y −3 2 0 96x), and the point at which it cuts the abscissa, defined as the theoretical renal phosphorus threshold, was 3 3 mg per 100 ml

TABLE I—FINDINGS IN PATIENTS WITH HYPERPARATHYROIDISM

Case no	Sex	Age (yr)	History of calculi (yr)	Serum-calcium		Plasma-ionised-calcium		Plasma-phosphorus		Urine-calcium (mg per day)		Creatinine-clearance (ml per min.)	Blood-urea (mg per 100 ml)	Renal phosphorus threshold (mg per 100 ml)
				No of tests	Range (mg per 100 ml)	No of tests	Range (mg per 100 ml)	No of tests	Range (mg per 100 ml)	Calcium intake normal	Calcium intake low*			
1	M	30	None	11	9·4–13·3	1	8·2	12	1·8–3·0	254–280	48	84	36	0·9
2	F	31	7	5	13·1–14·3	3	10·0–10·5	5	1·3–2·4	338–544	268	81	25	1·0
3	F	44	>4	10	9·5–12·5	5	6·2–7·3	10	2·0–3·9	464–482	193	80	34	2·0
4	F	48	25	8	9·6–12·3	1	7·2	8	2·9–4·0	248–270	175	73	46	2·0
5	F	55	1	1	14·4	1	9·6	2	2·3–2·4			73	39	0·8
6	M	61	13	2	9·8–10·5	2	5·4–6·4	3	2·5–2·8	273–293	92	72	46	1·4
7	M	64	4	5	11·0–12·1	2	6·2–6·7	5	2·4–3·0	238–446	130	89	35	1·6
Mean		47·6			11·96		7·65		2·5			79	37·3	

* Less than 150 mg calcium per day for 5 days

phorus corresponding to the point at which the regression line cuts the abscissa is defined as the theoretical renal phosphorus threshold. Results of a typical infusion are shown in fig 1.

Details of the infusion.—The buffered sodium phosphate (pH 7·4) comprised Na_2HPO_4 52·4 g and $NaH_2PO_4.2H_2O$ 11·5 g in 1 litre of sterile distilled water; this contains 1·37 g of inorganic phosphorus per 100 ml. The infusions were begun at about 10 A.M., with the patient fasted for 12 hours, and resting in bed. A linear rise in plasma-phosphorus was produced by injecting every 60 seconds a calculated volume of phosphate from a sterile graduated 20-ml syringe through polyethylene tubing into an arm vein. Initially we used the method of Anderson (1955a) for calculating the desired rate of infusion. We have since found it possible to inject an initial volume of 0·7 ml. per min., increasing progressively to 1·6 ml per min. at 180 minutes in most patients. If there were gross abnormalities in the size of the patient or the glomerular-filtration rate (G.F.R.), the rate of injection was adjusted by calculation. About 200 ml of the phosphorus solution (90 mM of P, 163 mEq of Na) was infused. A water diuresis was maintained by the patients' drinking 250 ml of water every 30 minutes. Urine specimens were obtained at approximately $^1/_2$-hour intervals, timed to the nearest $^1/_2$ minute. Women had an indwelling many-holed catheter inserted, and the bladder was washed out with sterile isotonic saline after each collection period. At the intended mid-point of each urine-collection period 8 ml of blood was taken from an indwelling needle in a limb not being used for infusion, mixed with 120 units of phosphate-free heparin, and centrifuged immediately.

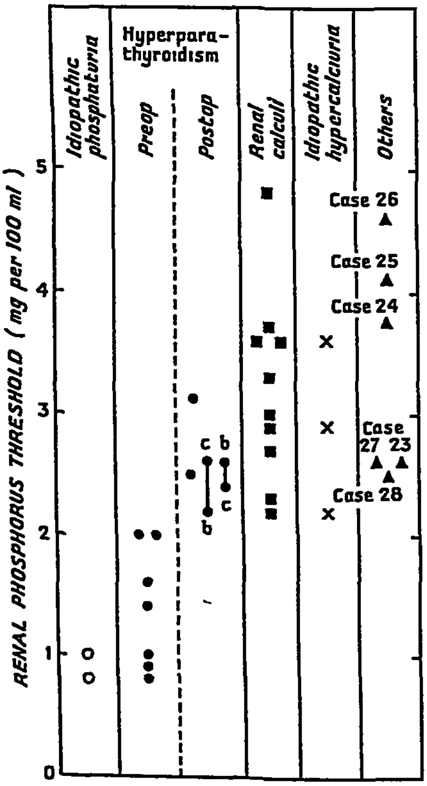

Fig 2—The theoretical renal phosphorus threshold in the twenty-eight patients investigated.

In the group of determinations after parathyroidectomy, the points coupled by a line represent two determinations in the same patient at (*b*) 11 days and (*c*) 5 months after operation. (See table VI.)

Other Investigations

Just before most of the infusions, blood was taken from the fasting patient for estimation of the serum-calcium, plasma-ionised-calcium, plasma-phosphorus, and plasma-creatinine. The creatinine output during each period of infusion, the pre-infusion fasting C_P/C_{Cr} ratio from 8 A.M. to 10 A.M., and the creatinine-clearance were determined; the P.E.I. was also calculated.

In twenty-one infusions the phosphate reabsorbed by the renal tubule was calculated in successive 30-minute periods; the difference between phosphate excreted in the urine (mg per min.) and in the filtered load (G.F.R. × plasma-P) was regarded as the reabsorbed phosphate. During the periods chosen the plasma-phosphorus level was higher than the renal-phosphorus threshold, and the tubular reabsorption of phosphorus was presumably maximal (Tm_P). In five patients the G.F.R. was measured by inulin infusion; in the remainder endogenous creatinine-clearance was used.

Analytical Methods

Calcium: Kramer and Tisdall (1921), and the Eppendorf flame photometer. Ionised calcium: Rose (1957). Phosphorus: Briggs (1922). Creatinine: Peters (1942). Urea: Peters and Van Slyke (1932). Inulin: Roe, Epstein, and Goldstein (1949).

Normal Limits

The following normal ranges have been established for this laboratory:

	Mean ± S D	*95% limits*	*80% limits*
Serum-calcium (mg per 100 ml)			
Kramer and Tisdall	9·9 ± 0·66	8·6–11·2	9·0–10·8
Flame photometer	9·3 ± 0·53	8·2–10·4	8·6–10·0
Plasma-phosphorus (mg per 100 ml)	3·6 ± 0·64	2·3–5·0	2·7–4·4

Plasma-ionised-calcium (mg per 100 ml): normal range 5·1–6·9 (16 determinations in eight subjects).

Values outside the 95% limits are regarded as definitely abnormal, while those between the 80% and 95% limits are suspicious; values within the 80% limits are regarded as normal. Serum-calcium levels determined by flame-photometry are marked with a dagger (†) in the tables. Normal values for the C_P/C_{Cr} ratio vary with the plasma-phosphorus level, and we have judged our results by the criteria of McGeown (1957). The normal range of P.E.I. is ±0·12 (Nordin and Fraser 1956); patients with hyperparathyroidism would be expected to give values higher than −0·12. Tm_P in fasting normal subjects on a normal diet is reported by Anderson (1955a) as 4·4–5·5 mg per min., and by Thompson and Hiatt (1957) as 73–199μM (2·3–6·2 mg) per min.

Results

The results are summarised in fig 2.

Group 1. *Hyperparathyroidism* (Cases 1–7, tables I and II)

a. Before Parathyroidectomy

The renal phosphorus threshold was 2·0 mg per 100 ml or less in all seven patients.

In four patients (cases 1, 3, 4, and 6) the serum-calcium was normal at least once during the preoperative period,

TABLE II—FINDINGS IN PATIENTS WITH RENAL CALCULI

Case no	Sex	Age (yr)	History of calculi (yr)	Serum-calcium		Plasma-ionised-calcium		Plasma-phosphorus		Urine-calcium (mg per day)		Creatinine-clearance (ml per min.)	Blood urea (mg per 100 ml)	Renal phosphorus threshold (mg per 100 ml)
				No of tests	Range (mg per 100 ml)	No of tests	Range (mg per 100 ml)	No of tests	Range (mg per 100 ml)	Calcium intake normal	Calcium intake low *			
8	M	25	>2	1	9 8	2	3 7–3 9	1	3 0			111		2 7
9	M	35	8	1	9 5	1	5 1	1	3 0			113		3 6
10	F	42	>1	3†	8 8–9 6	0		3	2 7–3 5			95	24	4 8
11	M	50	7	1†	9 4	1	5 3	1	2 3			103	35	2 2
12	M	51	3	4	9 8–10 8	2	5 3–6 2	4	2 4–3 4	92–154	44	67	44	2 9
13	F	59	1	4†	10 0–10 4	1	5 1	4	2 6–3 6	202–254		59	36	3 7
14	F	46	1	4	9 3–9 6	2	5·4–5 6	4	3 3–4 7	185–200		82	21	3 6
15	M	52	15	1	10 1	1	4 5	1	3 1				23	3 3
16	M	55	16	1	9 5	1	5 8	1	3 3				35	2 3
17	M	55	28	1	9 6	1	5 6	1	3 0				31	3 0
Mean		47			9 7		5 16		3 07			90	31	

* Less than 150 mg calcium per day for 5 days † By flame photometry

and on four separate occasions in case 1 when on a normal diet Case 6 had a consistently normal serum-calcium, but it rose to 11 1–11 3 mg per 100 ml after a low-phosphorus diet (610 mg per day) supplemented with aluminium hydroxide for 10 days

Whenever they were both measured, the plasma-ionised-calcium was normal when the serum-total-calcium was normal In particular, in case 6, the plasma-ionised-calcium did not exceed 6 4 mg per 100 ml (which is within our normal range, and that of 5 9–6 5 mg per 100 ml described by Lloyd and Rose 1958)

On the day of infusion, the fasting plasma-phosphorus at 10 A M was not definitely abnormal in six patients Repeated determinations (not necessarily fasting) gave at least one abnormal reading in three patients (cases 1–3), one patient (case 4) had a consistently normal plasma-phosphorus level, and three patients (cases 5–7) had levels that were never definitely abnormal

In the six patients studied, the urinary calcium excretion exceeded 250 mg per day on a normal diet In three of them the daily urinary calcium excretion fell to less than 150 mg when the calcium intake was reduced to less than 150 mg per day for 5 days, we regard this as a normal response (see Hodgkinson and Pyrah 1958) In the other three cases the urinary calcium excretion remained abnormal

In all cases the creatinine-clearance was within the range 72–89 ml per min The response to 5 units of pitressin tannate in oil intramuscularly was normal in one with a maximum urine specific gravity of 1024 (case 3), impaired in three (cases 4, 6, and 7), and not tested in the other three

The C_P/C_{Cr} ratio and the P E I were normal in case 1 on three occasions, and in case 4 on the only occasion it was measured Total plasma-proteins, alkaline phosphatase, and potassium were normal in all patients

b After Parathyroidectomy (table IV, fig 2)

The renal phosphorus threshold, redetermined in four patients (cases 2–4 and 6) 10–13 days after parathyroidectomy, was found to be more than 2 0 mg per 100 ml in each case There was no significant change in their creatinine-clearance, but the response to pitressin improved in the three patients in whom it was impaired before parathyroidectomy

The renal phosphorus threshold, reinvestigated in two patients (cases 2 and 3) 5 months after parathyroidectomy, was more than 2 0 mg per 100 ml

GROUP 2 *Renal Calculi* (Cases 8–17, tables II and IV)

The lowest renal phosphorus threshold found was 2 2 mg per 100 ml

The serum-calcium was definitely normal in nine patients and suspicious (10–10 4 mg per 100 ml by flame photometry) in one (case 13) Plasma-ionised-calcium was normal in the nine cases in which it was measured, including case 13 The fasting plasma phosphorus was normal in seven patients, and suspicious (2 3–2 6 mg per 100 ml) on one occasion in cases 11–13

Urinary calcium excretion was normal in the three patients investigated The range of renal function assessed by creatinine-clearance or blood-urea was similar to that of the patients with hyperparathyroidism The ratio C_P/C_{Cr} and P E I were normal in five cases (8–11, and 13), abnormally high in case 12, and not measured in cases 14–17

GROUP 3 *Idiopathic Hypercalciuria* (Cases 18–20, tables III and IV)

The renal phosphorus threshold was 2 2 mg per

TABLE III—FINDINGS IN PATIENTS WITH IDIOPATHIC HYPERCALCIURIA AND IN OTHER CONDITIONS

Case no	Diagnosis	Sex	Age (yr)	Serum-calcium		Plasma-ionised-calcium		Plasma-phosphorus		Urine-calcium (mg per day)		Creatinine clearance (ml per min)	Blood urea (mg per 100 ml)	Renal phosphorus threshold (mg per 100 ml)
				No of tests	Range (mg per 100 ml)	No of tests	Range (mg per 100 ml)	No of tests	Range (mg per 100 ml)	Calcium intake normal	Calcium intake low*			
18	Idiopathic hypercalciuria	F	39	8	9 4–10 9	1	5 1	8	2·5–3 7	260–445	68	91	29	3 6
19	,, ,,	M	43	4	8·9–10 4	1	5 3	4	2 8–3·9	556–635	340	117	31	2 9
20	,, ,,	M	46	6	9 3–11 2	3	4 6–5·0	6	2 7–3 2	398–460	106	87	37	2 2
21	Idiopathic phosphaturia	F	47	7	9 1–10 3	0		7	1 2–2 1	264		100	25	0 8
22	,,	F	56	3	10 1–10·4	0		3	1 0–2 2	45–110			22	1·0
23	Normal	M	19	1	10·9	0		1	3 2			151	34	2 6
24	,,	F	39	3	9 3–9·6	1	5 4	2	3 4–3 5			85	23	3 4
25	,,	F	60	1	10 2	0		2	3 2–3·4			59		4 1
26	Acromegaly	F	27	2†	9 5	0		2	4 3–5 2			125	20	4 6
27	,, (inactive)	F	62	2	10·4–10 8	1	5 2	2	3 1–3 5			87	26	2 6
28	Steatorrhœa and osteomalacia	M	61	2	7·4–7 9	0		3	1 3–2·6			95	25	2 5

* Less than 150 mg calcium per day for 5 days † By flame photometry

100 ml or higher in three patients with “idiopathic hypercalciuria”

In one patient (case 19) hypercalciuria persisted when the dietary intake of calcium was less than 150 mg for 5 days, in the other two the urinary calcium output fell to less than 150 mg per day

Case 20 had on one occasion a serum-calcium level of 11 2 mg per 100 ml, but it was normal on five other occasions Case 18 had suspicious serum-calcium levels (10 9 mg per 100 ml) on three occasions Plasma-ionised-calcium, plasma-phosphorus, C_P/C_{Cr} and P E I were never abnormal

GROUP 4

a Idiopathic Phosphaturia (Cases 21–22, tables III and IV)

The renal phosphorus threshold in two cases with a “renal phosphate leak” were among the lowest found in this series (0 8 and 1 0 mg per 100 ml) Both had consistently low levels of plasma-phosphorus, high C_P/C_{Cr} ratios, and high P E I The serum-calcium was normal

b Miscellaneous (Cases 23–28, tables III and IV)

Six other patients who had no evidence of hyperparathyroidism all had renal phosphorus thresholds above 2 4 mg per 100 ml Although case 28 had severe osteomalacia, bone biopsy showed “Wide osteoid seams are present There is no increased osteoblastic or osteoclastic activity” (Dr J L Pinniger) This helps to exclude secondary hyperparathyroidism

One patient with inactive acromegaly and mild pituitary insufficiency (case 27) had an abnormally high C_P/C_{Cr} and P E I

Measurement of Tm_P

In fourteen infusions the reabsorbed phosphate varied greatly in successive periods and the Tm_P could not be defined These fluctuations were not related to changes in G F R., and they occurred when both inulin and creatinine were used as measures of G F R There was no significant change in plasma-creatinine during any infusion Data from a representative group of patients are shown in table V

TABLE IV—COMPARISON OF INDICES OF PHOSPHATE METABOLISM ON THE DAY OF INFUSION (ALL AVAILABLE DATA)

Case no	Renal phosphorus threshold (mg per 100 ml.)	Plasma-phosphorus (mg per 100 ml)	C_P/C_{Cr}	P.E.I.
1 (*a*)	0 9	2 4	0 09	+0 02
2 (*a*)	1 0	2·5	0 30	+0 22
(*b*)	2 1	3 3	0 26	+0 14
(*c*)	2 6	2·9	0 11	+0 01
3 (*a*)	2·0	2 1	0 24	+0 19
(*b*)	2·6	2 9	0 21	+0 11
(*c*)	2·4	2 2	0 11	+0·05
4 (*a*)	2·0	4 2	0 27	+0 11
(*b*)	3·6	3 6	0 24	+0 11
5 (*a*)	0 8	2 5	0 65	+0 58
6 (*a*)	1 4	2 5		
(*b*)	2 5	3 6		
7 (*a*)	1 6	3 0		
8	2 7	3 7	0 23	+0 10
9	3 6	3 0	0 08	−0·02
10	4 8	3 5	0 12	−0·01
11	2 2	2 2	0 09	+0·03
12	2·9	2 4	0 24	+0 17
13	3 7	3 4	0 02	−0 10
18	3·6	3 3	0·07	−0·05
19	2·9	3 5	0 05	−0·08
20	2 2	3 2	0 14	+0·02
21	0 8	1 2	0·42	+0·41
22	1·0	1 8	0 52	+0·48
23	2 6	3 2	0·03	−0·08
25	4 1	3·4	0 08	−0·04
26	4·6	5 2	0 11	−0 10
27	2·6	3 5	0 30	+0 19
28	2 5	2 6	0 10	+0·02

a = preoperative.
b = 10–13 days after parathyroidectomy
c = 5 months after parathyroidectomy

TABLE V—G F R, TUBULAR REABSORPTION OF PHOSPHATE, AND RENAL PHOSPHORUS THRESHOLD IN SELECTED PATIENTS (SEE TEXT)

Case no	Range of G.F.R. (ml per min)	Phosphate reabsorbed in successive periods during the infusion (mg per min)						Renal phosphorus threshold (mg per 100 ml.)
2 (*a*)	73–82	1 1	1 2	1 6	1 8	2 6		1 0
(*b*)	88–95	2 6	3·0	3 1	3 2			2 1
(*c*)	67–74‡	2 0	2 4	1 9	1 6			2 6
3 (*a*)	75–90	1 4	1 5	1·4	1 6	1 6		2 0
(*b*)	70–76	1 9	2 0	2 0	1 7	1 7	2 2	2 6
(*c*)	69–75	1 7	1·5	1 7	1 9	1 4		2 4
4 (*a*)	68–76	2 3	2 6	2·4	3 3	3 6		2 0
(*b*)	63–75	2 5	2 7	3 5	3 1			3 6
13	52–62	1 8	1·4	1 1	1 1	1 2		3 7
20	83–94‡	2 4	2 1	2 6	2 1			2 2
27	80–93	2·0	1 3	1 4	0·4	0 6		2·5

a = preoperative
b = 10–13 days after parathyroidectomy
c = 5 months after parathyroidectomy
‡ Inulin-clearance.

The extremes of variability are shown in cases 2(*a*) and 27 In most cases showing a consistent trend, tubular reabsorption increased in successive periods, but in four (cases 2[*c*], 10, 13, and 27) it decreased

In cases 2 and 3 phosphate reabsorption had increased 10–13 days after parathyroidectomy, but in case 4 no significant change was detected, although the renal phosphorus threshold had increased considerably Moreover, in cases 2 and 3, the Tm_P 5 months after parathyroidectomy was indistinguishable from the preoperative value, while the renal phosphorus threshold had increased to within normal limits, and there was no evidence of active hyperparathyroidism

Results of Phosphate Infusion

The plasma-phosphorus level 15 minutes from the end of the infusion was 9–15 mg per 100 ml The mean rise in plasma-phosphorus achieved in hyperparathyroid patients was 7 mg per 100 ml, and in patients with renal calculi 8 7 mg per 100 ml

A fall in serum-calcium was noted in all infusions in which it was investigated, and it varied from 0 6 to 4 1 mg per 100 ml, the greatest falls being in patients who had high fasting serum-calcium levels In one patient with severe osteomalacia (case 28) the fall in serum-calcium from 7 9 mg to 5 2 mg per 100 ml was accompanied by tetany which responded to intravenous calcium gluconate

None of the patients experienced malaise, rigors, or venous thromboses

DISCUSSION

Theoretical Renal Phosphorus Threshold

Operation confirmed the diagnosis in all seven patients who had renal phosphorus thresholds of 2 0 mg per 100 ml or lower, and who were considered to have hyperparathyroidism

The renal phosphorus threshold was of particular value in three patients in whom at least two of the classical diagnostic criteria were normal Case 1 had normal serum-calcium levels on four of eleven occasions, had a normal urinary calcium output when on a low-calcium intake, had a normal C_P/C_{Cr} ratio and P.E.I on three occasions, and a normal response to two calcium infusions

(Nordin and Fraser 1954) Case 4 had a consistently normal plasma-phosphorus, and a normal C_P/C_{Cr} and PEI Initially case 6 had consistently normal levels of serum-calcium and plasma-ionised-calcium, but lowering the phosphorus intake did eventually elevate the serum-calcium above normal This patient also had a normal urinary calcium excretion when on a low-calcium intake

The fact that the renal phosphorus threshold rose to the normal range within 13 days of parathyroidectomy in the four patients tested indicates that it depends on parathyroid function It seems to be a valuable index for the identification of hyperparathyroidism in patients with renal calculi or nephrocalcinosis

We must point out that, with the exception of case 20, none of the patients with idiopathic hypercalciuria or idiopathic renal calculi were operated upon, and that there is slender evidence of hyperparathyroidism in some (suspicious levels of serum-calcium in cases 13, 18, and 20, and of plasma-phosphorus in cases 11, 12, and 13) but this diagnosis was considered very unlikely on all the available evidence

The renal phosphorus threshold is, of course, lowered in certain patients with primary disorders of renal tubular function (e g, cases 21 and 22), but these patients can usually be separated by the demonstration of defects such as aminoaciduria, glycosuria, or acidosis, and they lack other evidence of hyperparathyroidism

In the three normal patients (cases 23–25) the renal phosphorus threshold varied between 2 6 and 4 1 mg per 100 ml compared with Anderson's (1955a) range of 4 0–4 7 mg per 100 ml in six young adult males

Serum-calcium Levels

All seven patients with hyperparathyroidism had hypercalcæmia at some stage, although in case 6 this was only seen after a low-phosphate intake In three cases (1, 3, and 4) which were followed for 2–7 years, the hypercalcæmia was intermittent (compare Bogdonoff et al 1956, McGeown and Morrison 1959) Lloyd and Rose (1958) found increased ionised calcium and normal total calcium in two of seventeen patients with hyperparathyroidism, measurement of ionised calcium is, therefore, potentially a more sensitive index than measurement of total calcium, but in our experience it has not yet proved to be so (see also Loken and Gordan 1959)

Plasma-phosphorus Levels

The plasma-phosphorus levels overlap considerably between all four groups of patients, and, like many investigators (including Goldman et al (1957) and McGeown and Morrison (1959), we think this is an unreliable index of hyperparathyroidism

Impaired renal function may result in normal or raised plasma-phosphorus levels in patients with hyperparathyroidism From the data of Goldman and Bassett (1954), this seems unlikely when the GFR is higher than 50 ml per min All our patients with hyperparathyroidism had creatinine-clearances greater than 70 ml per min, and we consider that the frequent presence of normal plasma-phosphorus levels was not due to renal dysfunction but is a feature of the disease

Phosphate-clearance

Clearance of phosphate by the kidney shows much diurnal variation, is minimal at 8 A M., and is related to the plasma-phosphorus level (Stanbury 1958) The C_P/C_{Cr} ratio and the % TRP $\left(=\left[1-\frac{C_P}{C_{Cr}}\right]100\right)$ have been used to correlate the phosphate-clearance with GFR. Nordin and Fraser (1956) have related the clearance ratio to plasma-phosphorus as a PEI It is generally agreed that these indices of phosphate-clearance measured at endogenous levels of plasma-phosphorus do not unequivocally distinguish patients with hyperparathyroidism Thus we have found that the C_P/C_{Cr} ratio and PEI were normal in two patients with hyperparathyroidism and abnormally high in one patient (case 12) with renal calculi, and one with inactive acromegaly (case 27)

McGeown (1957) reported similar findings of normal C_P/C_{Cr} ratios in three out of thirteen proven cases of hyperparathyroidism, all of which had normal renal function These three patients and one other had a normal PEI Normal values of phosphate-clearance in hyperparathyroidism have been described by Kyle et al (1958) and normal % TRPs have been reported by Goldman et al (1957) and Thomas et al (1958)

The converse finding of abnormal indices of phosphate-clearance in the absence of any other evidence of hyperparathyroidism has been described by Nordin and Fraser (1956) and McGeown (1957) in patients with renal calculi, and by Thomas et al (1958) in patients with hypercalcæmia associated with myeloma or carcinoma

Maximum Tubular Reabsorption of Phosphate

When the plasma-phosphorus level is progressively raised, the quantity of phosphorus reabsorbed by the renal tubule will theoretically reach a maximum (the Tm_P)

Anderson (1955b) and Thompson and Hiatt (1957) have suggested that the Tm_P is lowered in hyperparathyroidism. There is doubt, however, about the constancy of Tm_P measurements

Anderson (1955a) demonstrated a Tm_P in six normal young adults studied carefully under basal conditions On the other hand, Longson et al (1956) found that in some subjects the phosphate reabsorption varied considerably during an infusion (perhaps because of alterations in GFR), and also varied from day to day in any individual Thompson and Hiatt (1957) describe similar findings, including changes possibly due to diet In our own experience the Tm_P has shown considerable changes during fourteen out of twenty-one infusions, particularly in hyperparathyroid patients This inconstancy has been noted with both inulin-clearance and creatinine-clearance as the measure of GFR

It has been noted above that the results in two patients before and five months after parathyroidectomy were indistinguishable Moreover there was no distinction between patients of group 1 (e g, case 4) and other patients (e g, cases 13 and 27) Reynolds et al (1959) report similar findings in eight proven cases of hyperparathyroidism Tm_P is clearly influenced by many factors, of which parathyroid function is only one, and it is therefore not the parameter of choice in assessing hyperparathyroidism

Conclusion

In this investigation the theoretical renal phosphate threshold has been the most useful single parameter for assessing hyperparathyroidism From the patients' point of view it is much quicker than studying the effect of low-calcium or low-phosphate intake, and it makes possible the investigation of inpatients within 24 hours

Summary

The renal phosphorus threshold has been shown to be abnormally low in hyperparathyroidism, and it is of particular value in recognising hyperparathyroidism in patients who only have renal calculi It may be abnormal when other parameters are normal

Other indices of phosphate excretion, based on plasma-phosphorus levels, phosphate-clearance, or maximal tubular reabsorption of phosphate, are less valuable

Our grateful acknowledgments are due to Mr J M Pullan, who performed all the parathyroidectomies on the patients under our care, to Dr H K Goadby for permission to study case 5, to Mr R. H O B Robinson and Mr T W Mimpriss for permission to study some of the cases with renal calculi, and to Dr J Hawkins, Mr R Hurst, and the staff of the William Dunn laboratory for their technical assistance

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CHOLESTEROL-BINDING CAPACITY OF SERUM GLOBULINS IN NORMAL AND ATHEROSCLEROTIC SUBJECTS

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WATER-INSOLUBLE hydrophobic cholesterol exists in a state of colloidal solution in biological systems The colloidal cholesterol-containing aggregates are complex structures with respect to size, configuration, and composition Their essential constituents are not only the plasma-lipids but also proteins—namely, α and β globulins (Chargaff 1944, Weinhouse 1943, Hueper 1945) Some qualitative alterations in the protein moieties of the cholesterol-containing micelles may occur, and this may influence atherogenesis (Katz and Stamler 1953) Indeed, electrophoresis (Barr et al. 1951) and ultracentrifugation (Gofman 1950, Gofman et al. 1950) have revealed such alterations in the lipid-containing micelles of the plasma

On the other hand, electrophoretic and biochemical investigations on atherosclerotic intimas showed that the lipid-containing globulins of atheromatous plaques are not normal, and that the lipid-binding capacity of these globulins is increased (Kayahan 1959) This shows that proteins are important in the pathogenesis of atherosclerosis

In atherosclerotic patients the absolute level of the blood-cholesterol is sometimes normal, but in people with high blood-cholesterol the incidence of atherosclerosis is high (Gubner and Ungerleider 1949, Gertler and Garn 1950) The purpose of this investigation was to determine the lipid-binding capacity of the serum globulins in normal subjects, in atherosclerotic patients with normal blood-cholesterol, and in patients with hypercholesterolæmia and arteriosclerosis

TABLE I—LIPID BOUND BY 1 G OF α-β GLOBULIN IN SERUM (MG LIPID PER G GLOBULIN)

Origin of serum		Cholesterol	Lipid
Atherosclerosis	Serum-cholesterol level		
Absent	Normal	98 (69–154)	472 (323–668)
Present	„	102 (72–167)	496 (342–688)
„	Raised	181 (165–263)	962 (743–1169)

Figures are means of 10 measurements with the ranges in parentheses

Materials and Methods

The cholesterol, total lipid, and α and β globulins were estimated, and the cholesterol and total lipid contents of 1 g of α-β globulin were calculated. The serum lipids were then extracted with ether Electrophoresis showed that this had not denatured the serum proteins significantly After the ether extraction, the total lipid and cholesterol remaining in the serum were estimated again. The lipid-containing ether was evaporated to dryness, and the lipid fractions were redissolved in the serum which was washed with ether These mixtures were incubated at 37°C for 20 hours They were then centrifuged at 3000 r p.m. for 30 minutes, and the undissolved lipids were discharged. Electrophoresis revealed that the added lipids were bound again to α and β globulins

The total lipid and cholesterol contents of the serum specimens were estimated again, and with these and previous values, the quantities of cholesterol and total lipid combined with 1 g of α-β globulin were calculated.

Results

Table I shows the quantity of cholesterol and total lipid bound to 1 g of α-β globulin in the serum of normal subjects and atherosclerotic patients The values for normal subjects were 98 and 472 mg, and the corresponding values for patients with atherosclerosis and high serum-cholesterol level were 181 and 962 mg

Table II shows the amount of cholesterol and total lipid combined with 1 g of α-β globulin of the serum in four groups of experiments

Conclusions

The tables show that there is considerable difference in the lipid-binding capacity of the serum globulins of normal subjects and of patients with hypercholesterolæmia and atherosclerosis The serum globulins of the latter combine with twice the amount of lipids extracted from the serum of either atherosclerotic patients or normal subjects The lipid-binding capacity of the serum globulins of normal subjects, on the other hand, is much less

The serum globulins of patients with atherosclerosis and normal serum-cholesterol levels behave like those of normal subjects

These results suggest that there are structural alterations of the serum globulins in patients with hyper-

TABLE II—CAPACITY OF SERUM GLOBULINS TO BIND SERUM LIPIDS (MG LIPID BOUND BY 1 G GLOBULIN)

Source of globulin		Source of Lipid	Bound cholesterol	Bound total Lipid
Atherosclerosis	Serum-cholesterol	Atherosclerosis		
Absent	Normal	Present	78 (49–95)	356 (224–507)
Present	„	„	82 (52–108)	402 (258–612)
„	Raised	Absent	148 (113–195)	774 (612–954)
„	„	Present	172 (128–215)	802 (635–[illegible])

Figures are means of 10 experiments with the ranges in parentheses cholesterolæmia Electrophoresis and ultracentrifugation of the serum lipoproteins also support this view On the other hand the lipid-binding capacity of the globulins of aortic intima has also been found to be increased in atherosclerosis (Kayahan 1959)

These findings support the view that the lipid-binding capacity of the globulins of the serum and intima may determine the plasma-lipid level and the lipid accumulation in atheromatous plaques of the intima, and that the metabolic changes of the lipid-binding globulins of the serum and intima may be of primary importance in the pathogenesis of atherosclerosis

I am grateful to Prof Sedat Tavat, head of the department of pharmacology and therapeutics, for his interest and encouragement in this work

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A SINGLE-DOSE TREATMENT OF THREADWORMS IN CHILDREN

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A HIGH proportion of town-dwelling children are infected with threadworms ("pinworms") and the majority apparently have unimpaired health (White 1956) However, the *Enterobius vermicularis* occupies the cæcum and appendix, and its relation to appendicitis has long been debated

That two common complaints may coexist is not surprising, but a causal relationship has not yet been firmly established, although Duran-Jorda (1957) provided good supportive evidence In a careful histological study of 691 excised appendices, he found that the 52 which contained threadworms were all inflamed, and he also demonstrated that the enterobius invades the substance of the appendix, causing a breach of the mucosa which would theoretically permit the entry of intestinal bacteria These findings accord with the views of Faust (1955), while Wilkinson (1959) believes that threadworm appendicitis is a clinical reality

Most cases of enterobiasis are treated for æsthetic reasons or because of perianal irritation, but, from the above evidence, it is arguable that treatment is also justified as a preventive measure

In treating enterobiasis with piperazine, White and Standen (1953a) achieved a cure-rate of 97%, using 50–75 mg per kg body-weight in divided daily dosage for seven days In the case of ascariasis, it has been established that single doses of piperazine citrate, phosphate, and adipate, equivalent to 4 g of piperazine hexahydrate, yield a cure-rate of over 80% (Goodwin and Standen 1958)

The action of piperazine has been studied by Standen (1955), who showed that pig roundworms, immersed in a modified Baldwin's solution containing a 1/560 concentration of piperazine citrate, were immobilised in six to twenty-four hours, yet continued to metabolise and recovered when removed and placed in a piperazine-free medium Goodwin and Standen (1954) also observed that specimens passed after piperazine treatment in man recovered when incubated at 37°C in piperazine-free Ringer's solution Since threadworms and roundworms are both nematodes it seems reasonable to suppose that the action of piperazine on both is similar

Bumbalo et al (1958) treated 37 infected children with a single dose of piperazine-citrate syrup (70 mg per lb body-weight, up to a maximum of 3 g) but could achieve a cure-rate of only 43%. They later obtained cure rates of 86% by giving a dose of 3 g , regardless of age, and repeating it after four days, and of 91% using a dose of 3 g on three consecutive days

Theoretically, the aim of treatment should be to maintain an adequate concentration of piperazine within the intestine long enough to ensure complete evacuation of all the paralysed worms by normal peristalsis However, there is considerable individual variation in intestinal motility, and Bockus (1944) has shown that in some people complete elimination of waste food-products from the bowel may take as much as four days In these "slow excretors" a single-dose treatment might fail, since parasites which have not been expelled may recover from the paralytic action of piperazine This possibility was recognised by Standen (1955) who, when treating ascariasis with a single dose of piperazine citrate, recommended the use of a purge in costive patients We thought that, in combination with a single dose of piperazine, standardised senna ('Senokot') would be more suitable than a saline purge, because its mode of action—namely, stimulation of muscular contraction of the colon through Auerbach's plexus—is physiological and reliable (Burgess 1958) Moreover, it is non-irritant (Douthwaite and Goulding 1957, Fairbairn 1958) and non-toxic (Hawkins 1958)

A palatable compound containing piperazine phosphate and standardised senna, in the form of flavoured granules ('Pripsen') was prepared and offered to us for evaluation We could hardly hope to exceed the cure-rate of 97% previously attained, but we thought that, with this preparation, the length of treatment of enterobiasis might be reducible without prejudice to the results

Investigation

Material and Methods

40 grains (2 6 g , approximately one-teaspoonful) of pripsen granules contain piperazine phosphate 1 g and standardised senna equivalent to 7 mg of sennosides A and B, in a flavoured base The control preparation contained an equivalent amount of piperazine phosphate, but no senna, it was almost identical in appearance and taste For the trial the two preparations were issued by the manufacturers in weighed doses, as compounds D and E, and their identity was not disclosed until the results had been analysed With each preparation, children of 2–5 years inclusive received 120 grains (3 g of piperazine phosphate) while those of 6–12 years received 160 grains (– 4 g) It was felt that in practice this scheme would be simpler than one based on body-weight

182 cases of enterobiasis were detected among medical and surgical admissions to the Evelina Children's Hospital, by identification of ova on adhesive 'Cellophane' swabs taken from the perianal region in the morning, before bathing and toilet (Graham 1941) Infected

children were treated alternately with compounds D and E, which were given at bedtime, accompanied by a drink or mixed with milk, water, or jam Perianal swabs were then taken on ten successive days, beginning on the morning after treatment.

We considered that (1) the rate of disappearance of ova after treatment would indicate the rapidity with which worms were expelled, and (2) during the first ten days after treatment the results would not be prejudiced by autoinfection, since maturation from ovum to oviposition is believed to take four to six weeks

Every slide was examined by an experienced technician and the appearance of one or more ova constituted a positive swab The criterion of cure was seven negative swabs (Mac Keith and Watson 1948), which meant that any child showing a positive swab after the third day was counted a failure.

Results

In 60 cases the child was discharged from hospital before ten post-treatment swabs could be obtained, and these cases have been excluded from the trial Of the 122 remaining for analysis, 59 had received pripsen and 63 piperazine phosphate alone 57 (97%) of the former and 58 (92%) of the latter fulfilled the criteria for a cure (see table), and of the cured cases, those treated with pripsen showed a more rapid clearance-rate (see figure) These differences, though not statistically significant, are in the expected direction.

Side-effects

Of the children treated with pripsen, 4 vomited during or immediately after administration, 1 was afterwards found to be cured and 3 had to be excluded. The majority had one to four soft or loose motions next day but only a few complained of abdominal discomfort. We have met only one instance of frank diarrhœa, occurring in a 4-year-old boy (not included in this trial) who was accidentally given 320 grains of pripsen (= 8 g of piperazine phosphate) He had completely recovered within twenty hours One child who received the control preparation had transient diarrhœa and vomiting and another complained of nausea On the whole both compounds were readily accepted by most of the children, and no systemic toxic effects were observed

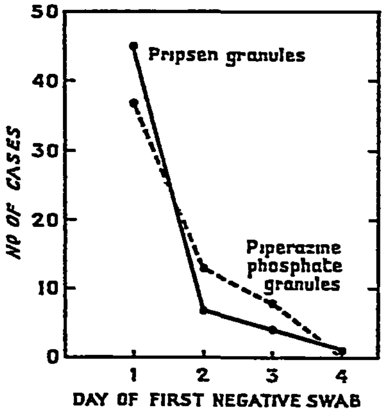
Discussion

These results show that a high cure-rate of enterobiasis can be achieved with a single dose of pripsen. Since, however, Bumbalo et al (1958), using a single dose of piperazine-citrate elixir, had a cure-rate of only 43%, we were somewhat astonished to find that in our control group, treated with granules of piperazine phosphate alone, the corresponding rate was 92% With a dose of 70 mg per lb body-weight and a maximum of 3 g, some of Bumbalo's cases almost certainly had a slightly smaller total dose than ours, but this may not be the full explanation of the wide discrepancy Standen (1955) found no difference in the in-vitro activity of piperazine citrate and phosphate solutions, but it is conceivable that the granular preparations used in the present trial may have physical properties which retard absorption from the alimentary tract and thus favour the maintenance of a higher concentration in the large bowel The absorption and excretion rates of this particular preparation have not yet been studied.

PERCENTAGE CURES

Treatment	Number of cases			% cures
	Total	Failures	Cures	
Pripsen	59	2	57	97
Piperazine phosphate	63	5	58	92

While the majority of the cured children showed no positive post-treatment swabs, a number gave positive swabs for one, two, or (in 1 case only) three days During this time some of these children must become reinfected, and treatment should therefore be repeated, the best time for repetition probably being one or two weeks after the initial treatment. With single-dose treatments the toxic effects sometimes described during seven-day courses (Sims 1953, White and Standen 1953b) have not been seen by either Bumbalo et al (1958) or ourselves In our trial the total dose of piperazine used in each child was less than half that hitherto used in a seven-day course.



The rate of clearance as indicated by the day on which the first of seven or more negative swabs was found.

With its high cure-rate, lack of toxicity, ease of administration, and simplicity of dosage, we regard pripsen as, at present, the remedy of choice for enterobiasis Fuller studies are needed, however, to determine the precise role of its senna component and also the pharmacological properties of the granular form in which the piperazine phosphate used in our trial was presented.

Summary

For treatment of threadworms the results obtained in 59 children given 'Pripsen' (a new granular compound containing piperazine phosphate and standardised senna) are compared with those obtained in 63 children given piperazine phosphate alone Though both preparations were given as single doses, the cure-rates were much the same as those reported with seven-day courses of piperazine

The doses of piperazine were less than half those hitherto used in seven days' treatment, and there were no toxic effects

Using a single dose of piperazine-citrate elixir, Bumbalo et al. (1958) had a much lower cure-rate, and further work is needed to elucidate the possible pharmacological advantages of the granular preparation of piperazine phosphate, as well as the precise part played by the senna component.

We wish to thank the consultant staff of the Evelina Children's Hospital for allowing us to treat their patients, the nursing staff for their constant help, and Mr F J Gibbs for examining the slides The pripsen and piperazine-phosphate granules were supplied by Westminster Laboratories Ltd

(*References overleaf*)

BIOCHEMICAL NORMALS IN NIGERIANS
URINARY 17-OXOSTEROIDS AND 17-OXOGENIC STEROIDS

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IN the course of routine analyses of urine from Nigerian patients at University College Hospital, Ibadan, it was observed that the urinary 17-oxosteroid excretion per 24 hours was significantly lower than values quoted in the literature and lower than was found in European patients In view of the increasing importance attached to the study of adrenal cortical hormones, it seemed desirable to find out the significance of these low values Assays were accordingly made on the urine of healthy Nigerian adults in order to establish normal values with which to compare the figures obtained from abnormal urine The results of this survey are here reported

Materials and Method

The subjects studied included forty-five male and fifty-five female Nigerians aged 20–30

Twenty of the males were laboratory staff (two doctors and eighteen student laboratory technologists) The other twenty-five males were labourers Thirty of the females were student nurses resident in the nurses' home at University College Hospital, Ibadan, while the other twenty-five were relations or wives living with the twenty males mentioned above The 24-hour urine samples were collected into Winchester bottles containing 10 ml of concentrated hydrochloric acid as preservative Creatinine excretion was measured in all the urine samples, only three showed a creatinine output of less than 1 g per 24 hours, and these were excluded from the series As a check on the methods, urine samples of six healthy male European laboratory technologists, aged 25–30, working at University College Hospital, Ibadan, were also analysed

Urinary 17-oxosteroids were determined by the method described by Moxham and Nabarro (1956) The 17-oxogenic steroids were estimated by Moxham and Nabarro's (1956) modification of the method of Appleby et al (1955), in which the pre-existing oxosteroids are destroyed with sodium borohydride, and the glucocorticoids are then oxidised with sodium bismuthate For the determination of creatinine in urine the alkaline-picrate method of Bonsnes and Taussky (1945) was used

Results

The mean 24-hour urinary output of the six Europeans was 16 5 mg for 17-oxosteroids and 15 4 mg for 17-oxogenic steroids These figures are near the values given by other workers (Barnett et al 1946, Moxham and Nabarro 1956) The urinary 17-oxosteroids and 17-oxogenic steroids in the Nigerians are presented in table I, adult males excreted about 50% more 17-oxosteroids than adult females The output of 17-oxogenic steroids was only slightly higher in males than in females (10%) The urinary output of 17-oxosteroids and 17-oxogenic steroids was about 35% lower in Nigerians than in healthy adult Europeans of comparable age This was seen in each sex

TABLE I—URINARY STEROID EXCRETION IN ADULT NIGERIANS (as mg per 24 hours)

Males	
17-oxosteroids	10 1±3 2 (4 1–20)
17-oxogenic steroids	10 6±2 7 (5 3–18 9)
Females	
17-oxosteroids	7 2±2 7 (4·0–15·0)
17-oxogenic steroids	9 7±2 0 (6 5–15·0)

To determine whether this difference has racial backgroud or whether it depends on socioeconomic factors, the Nigerian results were analysed into two income groups The results are shown in table II Group M_1 comprises the twenty male laboratory workers and M_2 the twenty-five male labourers F_1 comprises thirty student nurses, and F_2 the relatives and wives of group M_2 In both males and females, improvement in economic means produced significant increase in the mean urinary output of 17-oxosteroids and 17-oxogenic steroids The urinary excretion of 17-oxosteroids correlated more closely with income than did the urinary 17-oxogenic steroids The effect of nutrition was further demonstrated by measuring the 17-oxosteroid excretion in a male nephrotic at various levels of protein intake The dietary protein was changed weekly, and urine for steroid analysis was collected on the 6th and 7th days at each level of protein intake The results are shown in table III

TABLE II—EFFECT OF INCOME ON THE URINARY STEROID EXCRETION OF NIGERIANS

17-oxosteroids (mg per 24 hours)		17-oxogenic steroids (mg per 24 hours)	
M_1	M_2	M_1	M_2
12 7±3 8	8 3±1 7	12 1±3 7	9 4±1 6
0 001>P		0 01>P~0 001	
F_1	F_2	F_1	F_2
8 5±2 8	5 8±1 0	11 1±3 1	9 1±1 2
0 001>P		0 01>P>0 001	

Discussion

Barnicot and Wolfsson (1952) also found low urinary 17-ketosteroid-levels in Nigerians (average excretion 7 97±0 48 mg per 24 hours), and there was no difference between Nigerian students resident in London and a group of Nigerian labourers working at *Oshodi* Friedman (1954) and Ramachandran et al (1956) reported low values for Indian adults, and Lugg and Bowness (1951) found similar low values for Malayans in Malaya It is significant that all these people lived in areas of endemic undernutrition, especially as regards protein

The urinary neutral 17-oxosteroids reflect androgenic

TABLE III—EFFECT OF PROTEIN INTAKE ON THE 17-OXOSTEROID EXCRETION OF A MALE NEPHROTIC

—	Dietary nitrogen (g per 24 hours)	Urinary 17 oxosteroids (mg per 24 hours)
1st week		
Oct. 16–17	4·9	3 7 } Average 3·6
,, 17–18		3 5 }
2nd week		
Oct 23–24	15 2	5·0 } Average 5 5
,, 24–25		5 9 }
3rd week		
Oct. 30–31	23 6	7 7 } Average 8 0
,, 31–Nov 1		8 2 }
4th week		
Nov 6–7	32·0	8 7 } Average 8 5
,, 7–8		8 2 }

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functions, in the female they are produced entirely by the adrenal cortex, and in the male by the adrenal cortex and testes The testes contribute a third of the neutral urinary 17-oxosteroids The androgenic hormones have important metabolic effects, causing retention of nitrogen and phosphorus The urinary 17-oxogenic steroids measure the excretion of 17-hydroxycorticosteroids, which are important in the metabolism of protein, carbohydrate, and fat. In view of the role of the adrenal hormones in metabolism, it is not surprising that the production of these hormones, and hence the excretion of their metabolites, is in some way related to the nutritional state.

It has been suggested that the low steroid excretion in Africans is due to poor liver function and consequent failure to convert androgenic hormones efficiently into neutral 17-oxosteroids But a recent survey (Edozien 1958) revealed no evidence of impairment of liver function in apparently healthy Nigerians Further, Barnicot and Wolfsson (1952) found no significant difference in the mean values for the recovery of testosterone in Africans and Europeans The alternative explanation suggested by my data is that a dynamic relation exists between the level of food intake—and particularly protein—and the production of adrenal hormones

Summary

Urinary 17-oxosteroids and 17-oxogenic steroids in Nigerians have been studied. The mean excretion per 24 hours of 17-oxosteroids and 17-oxogenic steroids was lower than in Europeans

Among the Nigerians the urinary steroid excretion varied according to the socioeconomic background This should be borne in mind in evaluating the results of urinary steroid analyses in Africans and other subjects from areas of endemic undernutrition

I wish to thank Mr J M Pescod, F I M L T , for technical assistance, Miss L Bell, principal sister-tutor, University College Hospital, Ibadan, and Dr D Mendel, of the department of physiology, University College, Ibadan, for their cooperation over the samples, Dr Mendel for the figures for nitrogen intake from the nephrotic patient

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ALDOSTERONE AND HYDROCORTISONE SECRETION IN DEHYDRATION

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Oliguria or, in more severe cases, azotæmia is known to occur in dehydration As we have shown, both hæmodynamic and tubular factors contribute to the impairment of renal function As a result of the fall in blood-pressure and of concentration of the plasma (i e, increased colloid osmotic pressure) the filtration pressure in the glomeruli decreases (Gomori 1954, Gomori and Podhradszky 1937, Gomori et al 1939, Margitay-Becht and Gomori 1938) The reduction of glomerular filtration can clearly be shown by the clearance method (Gomori 1954, McCance and Widdowson 1937, Margitay-Becht and Gomori 1938, Takacs and Kallay 1957) The slowing of the circulation in dehydration is obviously followed by reduction of the blood-supply to the kidneys and deterioration of their function (Gomori 1954, Gömöri et al 1939, Takacs and Kallay 1957) At the same time tubules undergo anatomical changes which lead to the "passive" rediffusion of urea (Gomori et al 1949, 1954, Kenney 1949)

The question might arise whether humoral factors also contribute to the development of oliguria in dehydration We have shown that antidiuretic-hormone activity does not increase in dehydration, and thus increased antidiuretic-hormone activity is unlikely to be a factor (Gomori, Varga, and Jakab 1958) On the other hand, we have shown (Gomori, Gláz, et al 1958) by biological methods (Tait et al 1952) in dogs that, in dehydration following obstruction of the pylorus, aldersterone-like activity greatly increases in the blood of the adrenal-gland veins This increase may explain the reduction of sodium excretion—i e, oliguria Using likewise biological methods, Luetscher and Curtis (1955) found increased aldosterone-like activity in the urine of a patient with pyloric stenosis, and Bartter et al (1956) recorded this finding in patients with reduced salt intake and induced thirst According to these workers, reduction of extracellular space leads to the increase of aldosterone-like activity

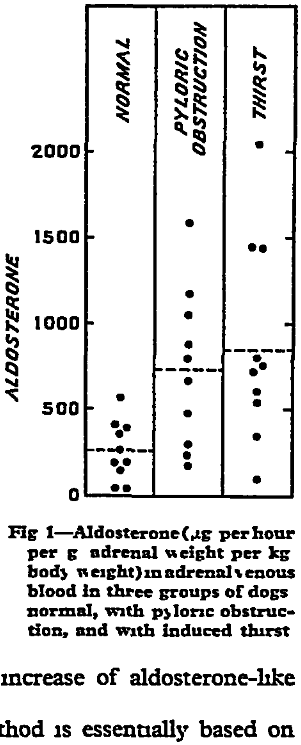

Fig 1—Aldosterone (µg per hour per g adrenal weight per kg body weight) in adrenal venous blood in three groups of dogs normal, with pyloric obstruction, and with induced thirst

Because the biological method is essentially based on the detection of a salt-retaining factor, it seemed desirable to determine both aldosterone and hydrocortisone in dehydration by quantitative chemical analysis

Accordingly we induced dehydration in dogs by obstructing the pylorus, as in our previous experiments (Gömöri and Podhradszky 1937, Gömöri et al 1939, 1954, Gömöri, Glaz et al 1958, Gömöri, Varga, and Jakab 1958), while another group of dogs was starved of food and water for 48 hours After 48 hours aldosterone and hydrocortisone were estimated in the blood of the adrenal glands In order to determine hormone secretion, the dogs were treated with heparin and were anæsthetised with chloralose Adrenal venous blood was collected by cannulating the left adrenolumbar vein with a polyethylene catheter located peripherally at the point of venous inflow from the left adrenal gland All tributaries to the adrenolumbar vein in this region—other than the adrenal veins—were ligated, and the adrenolumbar vein was obstructed at its junction with the inferior vena cava. By this procedure the flow of venous blood from the left adrenal gland was diverted from its normal path into the catheter

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The heparin-containing plasma thus obtained was extracted with ethyl acetate and, after alkali purification, shaken from a petrol-ether solution into 70% alcohol Aldosterone was isolated chromatographically, starting with the dried residue of the alcoholic extract Chromatography was carried out by the method of Moolenaar (1957) in two systems on Whatman no 1 paper Chromatography was followed by development with tetrazolium-blue, the developed formazon spots were eluted, and quantitative determination was carried out with a Beckmann B spectrophotometer

Observations were on ten control dogs Ten dogs were kept off water, and ten further dogs had their pylorus obstructed before the experiment

Our results showed that there was a considerable increase in aldosterone secretion in most of the dogs in which the pylorus had been obstructed, as in most of the dogs simply deprived of food and water, as compared with the secretion of the control dogs (figs 1 and 2) Statistical calculations show that the change is significant ($P < 0.01$) The increase in hydrocortisone is less unequivocal, the change cannot be termed significant ($P > 0.05$, Student test)

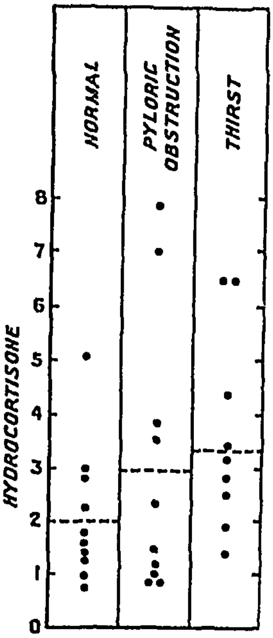

Fig 2—Hydrocortisone (µg per hour per g adrenal weight per kg body-weight) in venous blood from adrenal gland in three groups of dogs: normal, with pyloric obstruction, and with induced thirst

Our experiments indicate that increased aldosterone secretion is a factor in the reduced excretion of sodium in conditions of dehydration

Summary

Aldosterone secretion in the blood of the adrenal glands of dogs increased after obstruction of the pylorus or induction of thirst The change in hydrocortisone secretion was not significant

We wish to thank Miss Maria Paul for her kind assistance in carrying out the technical work

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“Medicine will become during the next ten years a more and more exact science The trend towards an increasing number of examinations using complex apparatus is bound to increase the cost of the health services Countries like the United Kingdom which enjoy a National Health Service must accept the idea that within the next ten years, real costs will be doubled, perhaps trebled” —Prof Zénon M Bacq, New Scientist, Jan 21, 1960 p 128

CHOLINE THEOPHYLLINATE IN CHILDREN WITH ASTHMA

A CONTROLLED TRIAL

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Assessing the effectiveness of treatment in asthma is difficult because of the many variables which may influence the condition Hence objective methods are necessary to measure the value of antispasmodic drugs

In a study of children with chronic pulmonary diseases (Strang 1960) it was shown that the ventilatory capacity in terms of the forced expiratory volume in 1 second ($F E V_1$) provided a satisfactory measurement of the asthmatic child's disability It was also shown that in the severe asthma of childhood, a persistent abnormality may exist over many months, and that asthmatic attacks more often arise as exacerbations of a subacute or chronic condition than they do from a previously normal ventilatory state The studies by Kennedy and Thursby-Pelham (1956, 1958) of the ventilatory capacity of asthmatic children during treatment with cortisone and prednisone revealed a similar kind of persistent impairment

In view of these findings, it seems reasonable to base the treatment of severe asthma on long-continued daily administration of drugs which reduce bronchial obstruction and improve the ventilatory capacity Gagliani et al (1954) and Turner-Warwick (1957) have shown that choline theophyllinate produces adequate blood levels of theophylline after oral doses, and that the levels are at least as good as those produced by other theophylline compounds

TABLE I—FAILURES TO ATTEND FOR EXAMINATION

Reason for failure	Lactose	Choline theophyllinate
Apparatus not available	2	11
Holidays	2	6
Illness	2	4
Total	6	21

An investigation of antispasmodic drugs by Gandevia et al (1957) showed that choline theophyllinate was effective in improving ventilatory capacity It causes less gastric irritation than aminophylline, and it has been suggested that it is most effective when administered over a long period (Dann et al 1954, Brown and Glancy 1955) We decided, therefore, to conduct a controlled trial of this drug, to measure its effect on the ventilatory capacity of children with severe asthma, when given four times daily for a prolonged period

The Trial

Fourteen children aged 7–13 years took part in the trial All were regarded as severe asthmatics and their parents said they were having attacks at least once every 3 weeks During the trial it became evident that most of them had a persistently impaired ventilatory capacity The trial started in September 1958, and ended in February 1959

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TABLE II—CHEST SIGNS ON AUSCULTATION DURING TREATMENT WITH LACTOSE AND CHOLINE THEOPHYLLINATE

Chest signs	Lactose	Choline theophyllinate
Present	48	29
Absent	42	46

$\chi^2=2{\cdot}971$, P>0 05

Seven children were given 1 lactose tablet four times daily for 3 months, followed by 1 tablet of choline theophyllinate four times daily for 3 months The other seven children started with choline theophyllinate for 3 months, and then continued with lactose tablets for 3 months The children were allocated at random to these two groups, and the investigator who saw them did not know whether they were having lactose or the trial drug

The dose of choline theophyllinate was 0 1 g for children under 10 years, and 0 2 g for children of 10 years and over The tablets were not identical in appearance, and the parents were told that the child was to have periods on two different drugs to find out which was better The parents were also supplied with ephedrine tablets (gr $^1/_2$) 1 of which was to be given if the child had an attack of asthma requiring treatment.

TABLE III—DYSPNŒA ON EXERTION DURING TREATMENT WITH LACTOSE AND CHOLINE THEOPHYLLINATE

Dyspnœa	Lactose	Choline theophyllinate
Present	44	30
Absent	46	45

$\chi^2=0{\cdot}972$, P>0·05

All the children were seen at 14-day intervals, but twenty-seven of the planned examinations were missed for various reasons Each time the F.E.V. $_1$ was measured, the chest was auscultated for the presence or absence of rhonchi, and a note was made of the number of attacks of wheezing and the presence or absence of dyspnœa on exertion

Results

Table I shows the numbers of planned examinations which were missed in each treatment group The difference between the two groups was largely due to the spirometer not always being available.

Clinical Data

At the end of the trial five patients thought that choline theophyllinate was more effective, two thought lactose was more effective, and seven thought there was no difference. The number of attacks of asthma in the two groups was compared by calculating the differences in the mean numbers of attacks per visit for each child in the two periods The mean difference was 0 43 attacks more in the lactose periods, and this did not differ significantly from zero ($t=0\ 322$, P >0 05) The frequency of rhonchi was not significantly different in the two groups (table II), nor was the frequency of dyspnœa (table III) No symptoms due to drug toxicity were observed

TABLE IV—SUCCESSIVE READINGS OF F E V $_1$ AS % OF NORMAL FOR HEIGHT IN EACH TREATMENT PERIOD

Case no	First 3-month period		Second 3-month period	
	Lactose	Mean	Choline theophyllinate	Mean
1	63, 64, 51 53, 66, 68	57 5	82, 68, 50, 50 73 75	66 3
3	78, 71 90, 65, 63, 60	71 2	69, 34, 29, 74, 77	56 6
5	51 55 81, 59, 50, 70, 67	61 9	85, 27, 61, 55 68, 72	61 3
7	78, 99 97, 50, 74, 90, 72	80·0	100, 76, 85, 75, 82	83 6
9	55 56, 62, 41 51, 60, 74	57 0	63, 81, 85, 75, 82	83 6
11	66, 32, 79, 40, 88, 64, 88	65 3	67, 88, 97, 88	85·0
13	22, 35, 34, 35, 21, 35, 43	32 1	82, 39, 45	55 3
		60·6		69 1
	Choline theophyllinate	Mean	Lactose	Mean
2	72, 59, 36, 47	53 5	50, 32, 45, 44, 56 59 17	43 3
4	113 113 110, 111, 111, 32 104	99 1	120, 121, 124, 110, 121, 127	120·5
6	30, 47, 45 45, 46	42 6	32, 36 37, 41, 31, 23, 38	34 0
8	77 79, 91, 89 73	81 8	83 85, 61, 60, 89, 91	78 2
10	69, 49 64, 53	58 8	44, 58, 63 63, 56, 54	56 3
12	63 59 61 33, 60, 44, 35 65	52 5	65, 64, 48, 61, 52	55 0
14	38, 34, 54, 43 31, 46	41 0	40, 36, 40, 35, 38, 45	39·0
		62 3		60·3

Mean F.E.V. $_1$ (% normal) first period (both treatments) = 61·4
" " " second " " = 64 3
Mean F.E.V. $_1$ (% normal) choline theophyllinate (both periods) = 65 6
" " " lactose " " = 60·5

TABLE V—ANALYSIS OF VARIANCE (1)

Source of variation	Sums of squares	Degrees of freedom	Variance estimate	Variance ratio (F)	P
Between treatments	1067	1	1067	5·45	<0·025
Between periods	360	1	360	1 84	>0·05
Interaction between treatments and periods	485	1	485	2·47	>0·05
High order interaction and variations between children	63,795	24	2658	13·58	<0·01
Residual	26,810	137	196		
Total	92,517	164			

Ventilatory Data

The F E V $_1$ results, converted to a percentage of the normal for height (Strang 1959), are presented in table IV They were treated by analysis of variance in two stages

The first form of analysis (table V) extracted from the total variation that due to the method of treatment, that due to the order of treatment, and that due to interaction between order and treatment. The variance-ratio test showed a significant benefit from treatment with choline theophyllinate It also showed that the effect of order was not significant, the performances in both periods being similar Finally, the order in which the drugs were given had no significant effect upon the response

TABLE VI—ANALYSIS OF VARIANCE (2)

Source of variation	Sum of squares	Degrees of freedom	Variance estimate	Variance ratio (F)	P
Between treatments	1067	1	1067	5·45	<0·025
Between Children	59,698	13	4592	23·46	<0·001
Interaction between children and treatments	4941	13	380	1·94	>0·05
Residual	26,810	137	196		
Total	92,517	164			

Because of the absence of order effect it seemed justifiable to ignore order The data were then reanalysed in a manner which would show any heterogeneity among the children in their reactions to the drug, and separate this from variation between individual mean performances This analysis, presented in table VI, shows that almost all the heterogeneity among children was due to variation between their mean performances, and that their responses to treatment were not significantly heterogeneous

Ten of the fourteen children had better mean performances with choline theophyllinate than with lactose

Discussion

Analysis of the symptoms indicated some benefit from choline theophyllinate compared with lactose, but the differences were not statistically significant nor were the children's parents strongly in favour of one or the other The ventilatory data, however, clearly showed benefit from choline theophyllinate, this was independent of the order in which the drugs were given, and, therefore, of changes in weather and patterns of respiratory infection during this period The response to treatment was reasonably uniform despite considerable variations in severity

The measurement of ventilatory capacity at regular fortnightly intervals provided a representative sample of a fluctuating condition. Failure of patients to attend for these examinations could bias the samples, but in the present investigation the failures to attend were almost entirely due to chance factors, and are unlikely to have influenced the result

The difference between the mean F E V $_1$s of children on lactose or on choline theophyllinate was significant but disappointingly small, and these children seem to need additional treatment of some kind We intend to assess other antispasmodic drugs and therapeutic procedures by a similar method Nevertheless, we may conclude that choline theophyllinate is an effective therapeutic agent although the benefit is small

Summary

As measured by the forced expiratory volume in 1 second, the ventilatory capacity of a group of fourteen children with asthma was altered favourably by the daily administration of choline theophyllinate

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MEPHENESIN POISONING

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WE describe here the clinical features and management of a patient who took an overdose of mephenesin

A housewife, aged 43 years, was admitted to hospital at 1 A M on Sept 5, 1957, as an "emergency", having been found unconscious at home one hour before Respiratory paralysis was diagnosed, and it was subsequently ascertained from her doctor that she had been given mephenesin ('Elixir Myanesin') some days previously on account of a chronic anxiety state The patient had taken an overdose, but the exact quantity could not be determined It was certainly not more than 6 fl oz and probably not less than 3 fl oz , so that the total mephenesin taken was somewhere between 5 5 and 11 g (She weighed 107 lb [48 7 kg]) She was not receiving any other medication at this time Six months previously she had taken an overdose of barbiturates, since when these drugs had not been available to her

The patient was comatose, but strong supraorbital pressure produced a slight response Respiration was abdominal and diaphragmatic, with intercostal paralysis Contraction of the accessory muscles of respiration was pronounced, the arms moving convulsively with each inspiratory effort Cyanosis was evident, and pharyngeal and tracheal secretions audible The blood-pressure was 110/80 mm Hg, pulse-rate 116 and regular, temperature 97° F The heart sounds were normal The pupils were moderately contracted and reacted to light, tendon reflexes were present in the lower limbs and not exaggerated, the plantar responses were extensor A catheter specimen of urine contained no glucose, acetone, albumin, or hæmoglobin

Management

The patient was taken to the operating-theatre, where tracheobronchial toilet was carried out and a cuffed oro-tracheal tube inserted without difficulty The cuff was then inflated and the tube connected to the "closed" circuit of an anæsthetic machine Assisted respiration was carried out using 2 litres of nitrous oxide to 3 litres of oxygen, with carbon dioxide absorption and a "spill-over"

As soon as good oxygenation was obtained, a large-bore œsophageal tube was passed into the stomach and gastric lavage carried out with normal saline solution.

Assisted respiration was necessary for more than two hours At 3 20 A M the intercostal muscles began to work and breathing became less laboured Accessory muscles were no longer being employed, and the colour remained good

The patient, still unconscious, was now disconnected from the anæsthetic machine, but the cuffed endotracheal tube remained in situ, tracheobronchial toilet being required occasionally

This state of affairs persisted for a further seven hours, during which respiration was adequate and the patient gradually emerged from coma. At the end of this period—i e , ten hours after the ingestion of the drug—the patient resented the presence of the endotracheal tube Following removal of the tube she was awake and would obey commands in a slow lethargic manner Over the next two hours she gradually became mentally alert and had no memory of events since the previous evening There were moist sounds throughout both lungs which cleared up in two days with penicillin and physiotherapy She was discharged from hospital on the fifth day, and has remained well ever since

Discussion

Goodman and Gilman (1955) state that the incidence of serious untoward effects caused by mephenesin is low They list the toxic effects as nystagmus, diplopia, lassitude, weakness, muscular incoordination, nausea, vomiting, syncope, sedation, and respiratory depression. Intravenous administration may cause phlebothrombosis, hæmolysis, hæmaturia and even anuria Robson and Keele (1951) cite several workers who have shown that mephenesin has a short duration of action because it is rapidly oxidised They state that in the rabbit very large doses cause paralysis of all muscles except the diaphragm Gray (1954) also mentions that very large doses in animals produce narcosis Goodier and Goodhart (1949) used a total of 39 ml of 2% mephenesin during a partial gastrectomy, and found that relaxation was never satisfactory

It would appear from this case that overdosage of mephenesin may produce more profound respiratory depression and sedation than has been supposed As it is being increasingly recommended for common conditions such as anxiety, tension states, and insomnia, it should be borne in mind as a possible cause in the differential diagnosis of respiratory depression or paralysis

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Preliminary Communication

BENCE JONES PROTEIN OF MYELOMA

THIS communication describes an observation on the atypical proteins associated with myelomatosis (Bence Jones proteins).[1]

Because of the shortcomings of the various heating and salt-precipitation tests for demonstrating the presence of these proteins, it is now common practice to separate the urine proteins by paper electrophoresis. When the proteins have been separated and the paper strip is stained by the methyl-green/pyronin method of Trevan and Sharrock[2] for ribonucleic and desoxyribonucleic acid, a deep reddish-purple band is found at the site of the abnormal globulin. Such a band has been demonstrated in 11 proven cases of myelomatosis. In all these cases a positive staining reaction was obtained in both serum and urine. For these studies the amount of serum seeded on to the filterpaper was 0·010 ml. When investigating urine samples it was found necessary to vary the amount of urine in order to obtain a well-stained band, using the usual protein-staining agent (azocarmine B[3]): generally 0·025 ml. of urine was sufficient, but occasionally it was necessary to increase this to 0·050 ml. The urine specimens were not subjected to concentration by dialysis, but were seeded directly on to the filterpapers.

The reaction has proved to be negative in about a hundred other electrophoretic preparations from cases of hyperglobulinæmia and proteinuria not associated with myelomatosis. These sera were derived from cases of liver disease, collagen diseases, renal abnormalities, and various malignant tumours. The specimens of urine were from cases with proteinuria ranging from simple albuminuria to the more complex protein losses associated with advanced nephrosis.

I suggest that the method of Trevan and Sharrock may be specific for true myeloma protein.

My practice is to make three electrophoretic preparations. In two the serum and urine are treated separately, and in the third the urine is seeded on top of the serum on the paper strip. This method permits easy comparison of the respective mobilities of the various proteins in serum and urine.

Further investigations are being made of the staining material associated with the atypical globulins, particularly with regard to its staining behaviour in the presence of nucleases.

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[1] Bence Jones, H. Phil. Trans. 1848, p. 55.
[2] Trevan, D. J., Sharrock, A. J. Path. Bact. 1951, 63, 326.
[3] Yeoman, W. B. Clin. chim. acta, 1959, 4, 523.

Reviews of Books

Brucella Infection and Undulant Fever in Man

SIR WELDON DALRYMPLE-CHAMPNEYS, C.B., D.M., F.R.C.P., late deputy chief medical officer, Ministry of Health, chairman, joint F.A.O./W.H.O. expert committee on brucellosis. London: Oxford University Press. 1960. Pp. 196. 25*s*.

Brucellosis in England

HUGH R. E. WALLIS, M.D., M.R.C.P., consultant pædiatrician, Bath clinical area. London: A. S. O'Connor. 1959. Pp. 140. 25*s*.

IT was over thirty years ago that Sir Weldon was instructed by the Chief Medical Officer at the Ministry of Health to inquire into the occurrence of undulant fever in England and Wales. Since that time he has read almost every word on the subject in many languages, he has talked to everyone who has a concern for this disease, and he has himself collected the available information on over 1500 indigenous cases. His findings and conclusions are now published in a small and elegant monograph. Here, without a wasted word, is all that anyone could reasonably want to know about a disease which may play only a small part in the Bills of Mortality but which remains of exceptional interest. This is not, we hope, the last word from this source, but it is a good foundation on which to base further inquiries.

Dr Wallis' book is less ambitious. He records his observations on 42 patients whom he suspects have had undulant fever and draws some dogmatic conclusions. The clinical descriptions are interesting. Some of his patients undoubtedly suffered from undulant fever, but many physicians will be unconvinced by his diagnosis in at least half of the patients. As Sir Weldon points out, the diagnostic value of a rise in the titre of agglutinins after an injection of brucellin is doubtful: the same phenomenon can be demonstrated in some apparently normal subjects. Therapeutic success is a dangerous diagnostic weapon, as the author admits, but some of his diagnoses seem to depend on little else.

In spite of these two books there is still a great deal to be known about this disease. About 1% of the adult population show agglutination titres of 1/160 or more: it is easy to guess that these are the result of past infections but of this there is no proof. It would seem dangerous to make the diagnosis (*a*) in the absence of other signs and symptoms, and (*b*) without either a demonstrated rise in titre or the cultivation of the organism from blood or marrow. It is possible that today milk-borne infections are the exception. Most urban milk is pasteurised. In one dairying district more than 70% of proven cases of undulant fever in the past ten years have been in those doing bovine midwifery (and these make up only 1–2% of the population). Of course they all drink raw milk—and so do 50% of the rest of the rural population—but on the farm undulant fever is a disease of the adults rather than of the children. It is indeed so much of an occupational disease that some form of specific immunisation might be of value.

There has recently been some alarm about the occurrence of infection with *Brucella melitensis* in cattle in England. It has not so far been transmitted to man and appears to produce a disease in cows indistinguishable from that caused by *Br. abortus*. To the bacteriologist the three species of brucella are distinct entities, but in fact aberrant and intermediate types occur not uncommonly. It is possible that had his material been drawn from other places the bacteriologist's classification might have been different. It has been general experience that Malta fever (due to *Br. melitensis*) is a more severe infection in man than undulant fever caused by *Br. abortus*. It is conceivable that the distinction depends not upon the bacterial species but upon some biological differences in the parasite which have so far escaped notice. Does passage through the goat enhance bacterial virulence? Does the severity of infection depend upon the dose received? And, for that matter, what is the minimum infective dose for man?

Horses are now luxuries and therefore denied the benefits of veterinary science enjoyed by cows and other useful animals. Before it is too late someone should investigate the curious story that *Br. abortus* is the principal cause of poll evil and fistulous withers in horses—i.e., deep-seated and chronic abscess formation. Generally speaking the pathological changes produced by natural infection with a bacterial parasite are much the same in all mammals. On the effects of S19 vaccine Sir Weldon is, perhaps, less than fair. Its introduction has certainly not yet reduced the number of human infections markedly, but the scheme is voluntary and even now less than half the calves born are inoculated. Since a cow remains a useful source of milk for many years, the effects of calfhood vaccination are not likely to be dramatic What is certain is that the number of abortions has fallen to less than a quarter, and it is said that at the moment less than 5% of the herds in the country are infected.

There is a lot to be learned from both these books—even if it is how little we know about a widespread disease

The Clinical Syndrome of Diabetes Mellitus

JOHN LISTER, M.D, M.R C P, consultant physician and physician in charge of diabetic clinics, Windsor group of hospitals London H K Lewis 1959 Pp 234 35s

THIS book fills a gap in the literature on diabetes mellitus, for it deals with the subject in enough detail to cover interestingly most facets of the syndrome and yet its size is limited to just over 200 smallish pages The script is enriched by a number of illustrations and photomicrographs, and there is a good brief historical introduction. Unfortunately there are also quite a number of inaccuracies and several omissions sulphonamides are not mentioned for the treatment of urinary infections, and the recommendations for intravenous therapy after surgery could lead to gross overloading with saline. Good bibliographies are supplied with each chapter, although they include by no means all the references cited in the text The book can be recommended as a useful summary of the clinical aspects of diabetes, but it should be possible to make several improvements for the second edition

Handbook of Circulation

Analysis and compilation PHILIP L ALTMAN Editors DOROTHY S DITTMER, RUDOLPH M GREBE National Academy of Sciences Philadelphia and London W B Saunders 1959 Pp 393 52s 6*d*

HERE is tabulation in an extreme form This book contains no text, only tables and a small number of diagrams with explanatory notes and lists of references The tables contain an enormous amount of information about every conceivable aspect of the circulation in man and animals (including birds and fish), and even translocation in plants Unfortunately, much of the material is unsuitable for tabular presentation, and generally the chief aim seems to have been to achieve comprehensiveness rather than the clear presentation of critically assessed information The figures are often disappointing

The list of contributors, containing 326 names, reads like a *Who's Who* of American cardiology, and also includes a few authorities of international renown from other countries Such a large number may perhaps have been necessary to collect the huge volume of material, but the quality of the end-result uggests an overabundance of cooks Nevertheless the volume has undoubted value as a source of references and as a quick means of discovering whether anybody has yet published measurements of almost any parameter of the circulation in plants, animals, or man.

Soil, Grass and Cancer

ANDRÉ VOISIN, membre de l'Académie d Agriculture de France, chargé d enseignement a l'École Nationale Vétérinaire d'Alfort (Paris) London Crosby Lockwood 1959 Pp 302 30s

THE author of this book believes that the trace elements, particularly copper, and the mineral balance of the soil play a fundamental part in the welfare of animals and human beings Few would dispute this, but most experienced agronomists and physiologists will feel that in this clever and well-documented book he has overplayed his hand In spite of the 428 references to original papers and books, which imply a profound knowledge of the subject, he presents a picture which will strike some people as lacking just that balance which he appears to revere so much in Nature The titles of his chapters ell their own story Thus we are reminded that we are dust, hat a disorder of copper metabolism is one of the causes of cancer, that there are milks which produce idiots, and that tronomic original sin is the principal cause of the mental llness of our children. This is strong medicine!

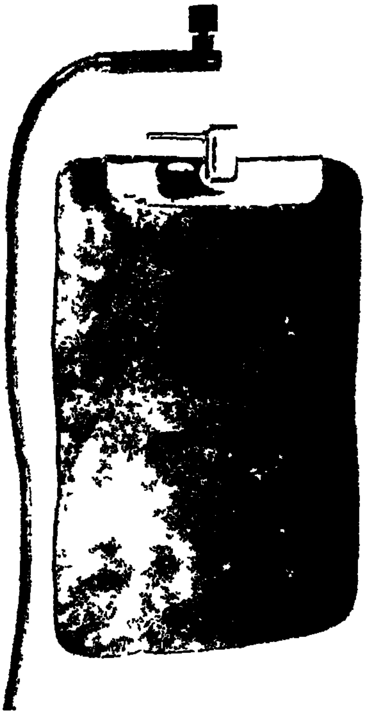
Experienced investigators, however, particularly those with wide interests, will find much to stimulate their minds in this book, and it will no doubt appeal strongly to those who believe that Nature, whoever she may be, is always right and "man" is generally wrong! The book is not likely to find a ready sale among the medical profession, and it cannot be recommended for general reading without the proviso that, even if the author is not a "crank" (and we have the assurance of a scientist in the foreword that he is not), any disciple of his may very well turn into one

Rheumatic Fever (*A Handbook for Parents* London Empire Rheumatism Council, Faraday House, 8–10, Charing Cross Road, London, W C 2) —This six-page booklet is praiseworthy because of the importance it gives to prevention of recurrences of rheumatic fever and of subacute bacterial endocarditis by the wise use of penicillin. In places it has a somewhat old-fashioned air, which might make parents anxious while leaving some reasonable questions unanswered It is free and obtainable (by doctors only) from the above address

New Inventions

A SAFER DIATHERMY PLATE

THE indifferent electrode of the surgical diathermy machine receives little attention unless it causes trouble in the form of an electrical burn Occasional accidents of this kind have been traced to faults in the terminal of the electrode, or of its lead For example, the insulation between the lead and the terminal may wear and expose the underlying cable, the terminal itself may become detached from the plate and therefore transmit the whole of the current at a localised point, or the terminal may cause a deeper impression than the rest of the plate and thereby transmit a higher concentration of current



To overcome these dangers and reduce the risk of a diathermy burn, the plate illustrated (see figure) has been in use at Southmead Hospital, Bristol, for the past two years This plate has a male terminal, and the lead has a completely insulated female terminal If the lead comes adrift from the plate, there is no exposed portion to transmit the current, since the whole lead (including the clamping screw) is covered by insulating material The lead also has a double thickness of insulation from its terminal for a distance of about 18 in, the outer layer of which is transparent so that any fault at the junction of the lead and terminal can be seen easily

I am indebted to the Endoscopic Instrument Company, of 62, Shirland Road, London, W 9, for help with the design and manufacture of this plate

Southmead Hospital
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J P MITCHELL
M.S Lond, F R C.S E, F R C.S

THE LANCET

LONDON 30 JANUARY 1960

Medical Needs of India

India has been standing on her own feet for twelve years, and in this short time her leaders have made a brave attempt to establish a Western-style democracy and bring her people into the garden of political maturity As the only Asian country to try to do this, India has great opportunities, but both people and leaders are having to face realities from which they were long protected "Independence" (the words "freedom" or "liberation" are not quite polite in India) has not removed or solved basic problems in the economic, social, or political spheres Indeed, some of these have been exacerbated by recent developments, including the accelerated increase in population

The medical profession is certainly to some extent responsible for this population pressure, but we have no need to be ashamed of that, provided that we help to cope with the consequences At present the success of efforts to raise production is just about balanced by population increase, and the average standard of living remains appallingly low—how low can only be understood by those who have lived and worked in the country It is perhaps unfortunate that so few British people have ever done this, except under the artificial conditions of war-time One of the most depressing features of the world situation is that while the developed nations are becoming richer many of the others are still becoming relatively poorer The people of the poor countries are well aware of this, but we in the rich ones are too often content to give thanks that we are not as other men

For specifically medical problems, the Government of India has inherited a health service, including teaching hospitals and schools which were British-organised but have long been staffed almost entirely by Indians, mostly trained in India. Unfortunately, however, this great service was organised along semi-military lines seniority within it determines status, and status is interpreted in a military sense Even university chairs are included in the grades There is a director of medical services in each State and a director-general at the centre, and their rule is no fiction they can and do post senior people at pleasure, and determine in detail the staff of every hospital, school, or research institute There is no open competition for appointments, and the methods of administration are rigid and old-fashioned There are no local committees, medical or lay, to soften its rigours and spread a sense of responsibility One would have expected this to have been changed after Independence, but it certainly has not It is much to the credit of Indian doctors that their sense of duty to their patients is so strong, especially to the illiterate and semiarticulate who constitute the great mass General practice is outside the service, and naturally many of the more intelligent young people enter private practice as soon as they can

On the credit side there has been a big effort to train more doctors, especially by the opening of new schools No attempt has been made to introduce grades with inferior training, and the standard of qualifying examinations is being maintained with a central pool of external examiners This has meant abolishing certain of the State diplomas and closing some of the older substandard schools, some of which were run by Christian missionaries Though some of the missionary hospitals and schools were outstandingly good and these continue—for example, Vellore, which has plenty of candidates for its medical school—the Government does not look with favour on missionary effort. On the other hand, there is political support for Ayurvedic medicine —a system which is based on the old four humours and employs cheap herbal remedies The students of Ayurveda are not, as might be imagined, humble villagers any more, but smart young men in Western trousers with tucked-in shirts who carry stethoscopes and frequent well-built modern hospitals and colleges There is much support for all this on nationalistic and religious grounds, even from distinguished "allopaths" themselves On the other hand, there is little remaining prejudice against Western medicine, even among the more backward

Postgraduate training is being expanded greatly, especially at new institutes which are attached to large specialist hospitals in the main centres and integrated with the local universities This decentralisation allows more doctors to have instruction at less expense than in the vast central institute that was at one time proposed (The whole scheme goes back to a committee formed in 1941 under the chairmanship of the late Sir BENNETT HANCE) Many specialties are still undermanned by Western standards—e g, anæsthesia and pathology The new institutes are sensibly built to suit the climate of their locality indeed, most are somewhat makeshift adaptations—frankly utilitarian and making no attempt to dazzle the foreign visitor Entry to them is open only to members of the health service, arbitrarily chosen from above

Not only has the supply of medical manpower to be considered, but also its distribution This is extremely uneven, the larger centres being overdoctored while the backward countryside, where most of the real work is to be done, relies on such expedients as midwifery by the village barber's wife There is nothing—apart from a sense of duty worthy of a saint—to attract doctors to the *mofusil* Pay is execrable, no special facilities are granted for travelling or housing, no prospect is given for refresher courses or promotion, and professional and cultural isolation may be almost complete Even in the cities pay is so poor that part-time private practice is essential, while young practitioners are attracted abroad by better prospects. Moreover, a large proportion of Indian doctors still want to stay at home and live in the old way with all their relations under the same roof. To have a hobby is regarded as a serious eccentricity, and this applies especially to such things as field sports, gardening, or the study of natural history—to enjoy which some Europeans will endure, or even welcome, isolation.

The content of practice approaches nearer to the European now that purdah has virtually vanished (it was a Muslim importation) and the tropical diseases are within the range of eradication, though there is a great deal to be done with them yet. Rational nutrition is much limited by the sacredness of the cow, and the elementary rules of hygiene are disregarded. On the other hand, when malnutrition and epidemics become less overwhelming, conditions that used to be thought unusual in India grow more conspicuous—for example, rheumatic fever (even in the hot parts of the country) and especially tuberculosis. The importance of family planning is becoming appreciated and Hinduism raises no religious bar to this. As a corollary, child health is of growing interest to the younger parents.

Textbooks are relatively scarce. Indian printing and publishing are improving enormously in quality and quantity, but they have not yet caught up with the old-established British firms, and few Indian textbooks have been written. Fortunately English is still the common language of educated Indians, and they use British textbooks, but far more use of such works would be made if more of them could be brought within the means both of students and of teachers. Libraries are often good but cannot cater for the demand, nor can the few libraries of the British Council, which hold the only available copies of many important books, especially for postgraduates.

As for practical help, it is much less easy nowadays for European doctors to settle in India: even medical missionaries are being slowly eliminated as replacements fall due, fewer being allowed to enter than to leave. But active help for limited periods with specific projects is needed urgently, and under such schemes as the Colombo Plan this can often be given without prejudicing a career at home. The work can be deeply interesting and rewarding, and from all points of view it is a great pity that there should be difficulty in finding people to go. Lecture tours by the eminent, however acceptable, are no substitute for actual work in the country. At home, we can continue to welcome Indian doctors who come for postgraduate study, whether for specific courses or to work here temporarily, and must try to understand their difficulties when uprooted from their own social environment, especially coming from a land where family, social, and religious ties mean so much. There is sometimes a regrettable tendency to treat senior Indians as though they were juniors: they can teach much wherever they go, and more exchange professorships ought to be arranged for them. On the more commercial side, we could help to provide more textbooks and well-designed equipment. British manufacturers of sound drugs and equipment are not always well represented in India—in the face of competition from other countries which is not always as ethical as their own methods or products. None of this, however, is a substitute for personal visits in both directions, of a length sufficient to reveal helpful attitudes and common ground. Such visits can also show that our ways of control and administration are not as rigid as most Indians suppose.

India is a great country striving hard to advance despite an enormous burden of poverty, ignorance, prejudice, and indifference. Her doctors, in common with other professions, still look to Britain for guidance and with respect. We are losing a great opportunity if we do not respond.

Common-cold Viruses

AFTER 13 years of painstaking study at the Common Cold Research Unit it now seems likely that Dr ANDREWES and his colleagues have succeeded in propagating—and what is more important, recognising in vitro—viruses derived from patients with colds. Prior to the work they describe in the opening pages of this issue, the only means of recognising common-cold viruses was their ability to induce colds in a proportion of human volunteers. Indeed one of the major achievements of the Salisbury workers has been the devising of techniques that enable meaningful experiments to be done with human volunteers.[1] Now, after many failures with orthodox conditions of tissue culture and with a variety of methods of detecting virus action, success seems to have been won.

Human volunteer experiments suggested that two agents (P.K. and H.G.P.) capable of causing colds were propagated in human embryo kidney cells maintained at 33°C in synthetic medium 199,[2] so an intensive search for an in-vitro method of detecting virus was started. HITCHCOCK and TYRRELL (p. 237) showed that tissue cultures supposedly infected with Salisbury cold viruses interfered with the growth of a hæmagglutinating virus added 4 to 5 days later. Thus, when tissue cultures inoculated with cold virus were subsequently infected with Echo 11 or Sendai (parainfluenza) viruses, the yield of hæmagglutinin was significantly less than in control tubes of previously infected human embryo kidney cells. This enabled the simple in-vitro test to replace cumbersome human volunteer experiments for detecting virus. In this way it was found that the addition of glucose and bovine albumin to the 199 medium improved the propagation of the interfering agent. Using this technique, two agents were isolated from nasal washings of 4 patients examined. Virus was isolated from nasal washings in the acute but not the convalescent phase. Later, TYRRELL and PARSONS (p. 239) found that at least 3 strains (H.G.P., P.K., and S.E.B.) of virus isolated from common colds could cause cytopathic changes in human embryo kidney cells, and 2 of them (H.G.P. and P.K.) in monkey kidney cells as well. This observation sprang from an accident trouble was experienced with toxicity in a batch of medium 199, so a new supply was secured, this happened to contain only 0 09% instead of 0 16% sodium bicarbonate, and cells in this medium showed a cytopathic effect when inoculated with H G P virus It seems that the low bicarbonate level was the all-important factor Now, sparsely grown second-generation monkey kidney cultures grown in Hanks' solution, lactalbumin hydrolysate, and 2% calf serum with 0 03% sodium bicarbonate is the preferred culture system Foci of degeneration appeared in 2 to 7 days and spread to involve the whole culture 5 to 10 days later This is a technical advance of first-rate importance As the Salisbury workers point out, their strains have not yet been conclusively shown to be common-cold viruses But careful controls to exclude the possibility of picking up a stray virus were included at every stage, also the properties (size, ether resistance, pH, and heat sensitivity) of the agents recognised by volunteer experiments, interference, and cytopathic effect are very similar The means now at hand both for tissue-culture study and human volunteer experiments should not leave this matter long in doubt. It will also be possible to determine whether the Salisbury viruses are all antigenically related to each other and what relationship they bear to other recently isolated viruses

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[1] Andrewes, C. H. New Engl. J. Med. 1950, 242, 235.
[2] Morgan, J. F., Parker, R. C. Proc. Soc. exp. Biol., N.Y. 1950, 73, 1.

In the past decade well over 70 new viruses have been isolated from man, and many of them—notably the new members of the myxovirus (influenza), enterovirus, adenovirus, and reovirus groups—can cause severe and mild respiratory illnesses [3–5] The symptoms of infection of the respiratory tract are relatively few, and, since one virus type can cause both severe and mild disease, many authorities, particularly in the United States,[6] believe that these new viruses probably account for a significant proportion of common colds In view of their failure to isolate any of the new viruses—despite adequate technique—from their patients with colds, and also because they have failed to reproduce colds consistently in volunteers infected with these newer respiratory viruses, the Salisbury workers [4] have felt that the agent of common colds in adults as studied by them has yet to be identified Moreover, they have inclined to the view [4] that the commonest variety of common cold in adults is a distinct entity caused by a distinct virus or group of related viruses The clinical features of this sort of afebrile cold have been described by RODEN [7] and consisted mainly of increased nasal discharge

HOPE SIMPSON's careful inquiries [8] showed that many adults had as many as seven colds a year He also noted that there are many features of the epidemiology of colds which are inexplicable by the theory of simple transmission, and he brought forward evidence suggesting that relative humidity was a very important factor Thus, a low humidity favoured the development of the clinical manifestations of a cold—perhaps (though this is sheer speculation) in a way analogous to the influence of low bicarbonate levels in making manifest the cytopathic effect of the Salisbury virus on tissue culture The demonstrated capacity of the Salisbury viruses to interfere with Sendai or Echo-11 viruses may perhaps mean that the Salisbury strains will themselves turn out to be susceptible to interferon—the recently described mediator of viro-interference which has many of the properties of a viral antibiotic.[9] Thus, it could conceivably be that these researches are pointing to both the cause and the cure of the common cold But as our contributors declare, great caution is required in assessing their results at this preliminary stage. It has yet to be shown that these viruses cause colds, let alone all colds, and experience in virus diseases teaches that there is a very long delay between the discovery of the cause of a disease and the elaboration of adequate means for its control The Salisbury workers are to be congratulated on taking a distinct step forward, and it is to be hoped that the pace of advance will now quicken against this tiresome and economically important malady

B.C G. Vaccination

THE second report to the Medical Research Council on B C G and vole bacillus vaccines [10] should have removed any remaining doubts [11] about the ability of these vaccines to prevent tuberculosis in young people. Under the strictly controlled conditions of the trial the reduction in the incidence of tuberculosis over a five-year period that could be attributed to the vaccines was 83% for B C G and 87% for vole vaccine. There seems no reason why similar reductions should not be obtained in this country when the vaccines are used under ordinary field conditions The Ministry of Health authorised B C G vaccination of 13-year-old schoolchildren in 1953, and SPRINGETT [12] has reported the effects of this scheme in Birmingham

Vaccination of schoolchildren began in 1954, and all those reaching 14 years of age in or after March, 1955, should have been included in the scheme, so in 1958 all aged 14 and 15 had been eligible for tuberculin-testing and vaccination, together with almost all aged 16, a large proportion of the 17-year-olds, and a few of those aged 18, but none over that age Each year, of some 15,000–17,000 children who left school, roughly three-quarters received their parents' consent to take part in the scheme, and over 85% of those tuberculin-tested were found negative and were vaccinated In 1954, when vaccination began, there were 231 notifications of tuberculosis in Birmingham in persons aged 10–19 years, the corresponding figures for the next four years were 203, 154, 119, and 143 Children aged 14 were fully covered by the scheme from 1956 onwards, among them there were 19 notifications in 1955, 8 in 1956, and 6 in 1958 Those aged 15 were covered from 1957 and the number of notifications among them fell from 24 in 1955 to 3 in 1958 The reduction in the total notification-rates possibly attribut-

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[3] Huebner, R. J Perspectives in Virology, p 121 New York

[4] Andrewes, C H *Brit med Bull* 1959, 15, 225

[5] Sabin, A B *Science*, 1959 130, 1387

[6] Huebner R J Rowe W P, Chanock, R M *Ann Rev Microbiol* 1958, 12, 49

[7] Roden, A T *Proc R Soc Med* 1958, 51, 271

[8] Hope Simpson, R E *ibid* p 267

[9] Isaacs, A Burke, D C *Brit med Bull* 1959, 15, 185

[11] Medical Research Council Tuberculosis Vaccines Clinical Trials Committee *Brit med J* 1959 ii 379

[12] Andersen A S, et al *ibid* 1959, i 1423

[13] Springett, V H *Tubercle, Lond* 1959, 40, 432

able to the B.C.G. vaccination scheme was estimated to have been 0.5–0.7 per 1000 per year.

The value of a B.C.G. scheme in a community depends on the proportion of individuals in it who are already infected at the age when vaccination is offered and the risk of infection after vaccination. In the M.R.C. trial (and in others) the incidence of tuberculosis in the observation period was highest in those who were tuberculin-positive on entry. This is, of course, not surprising, for tuberculin sensitivity in such circumstances indicates tuberculous disease, even though there are no other observable manifestations of it. But in assessing the benefits of vaccination, the spread of the lesions in this already infected group must be taken into account. It was estimated that, if all those tuberculin-negative on entry to the M.R.C. trial in 1950–52 at the age of 14 had been vaccinated, the reduction in tuberculosis among the whole group, both tuberculin-negative and tuberculin-positive, would have been 59% in the next five years. Since 1950, however, the risk of infection in this country had decreased. SUTHERLAND,[13] taking this decrease into account, has estimated the present scope for B.C.G. vaccination in England and Wales. Of the tuberculosis notifications in those aged 15–19 in 1958, he estimates that 52% could have been prevented if all who were tuberculin-negative at the age of 14 had then been vaccinated: the estimate for 1953 was 60%. While decline in exposure to infection continues, the scope for vaccination will also decline. B.C.G. vaccination of all uninfected who are now aged 14 would apparently reduce the incidence of tuberculosis in this age-group during the next five years by rather less than half. Although the decrease in the *proportion* of cases preventable has been slight in the past five years, the decline in the *numbers* has been great—from about 2950 among those aged 15–19 in 1953, to 1400 in 1958. A stage may fairly soon be reached where mass vaccination of older schoolchildren prevents only a few cases of tuberculosis in young adults, although vaccinations done in the past will, if protection is maintained, still be preventing tuberculosis in those over 20. SPRINGETT suggests that communities using B.C.G. vaccination in older schoolchildren should continue the procedure until notification-rates in the non-vaccinated groups are down to 0.1 per 1000 per year.

SUTHERLAND has also estimated the reduction in incidence of tuberculosis in those 15–19 years old which resulted from the local-authority vaccination schemes. In 1958, for example, the reduction was 211 notifications. But the number preventable if all children eligible had been vaccinated was about six times as large. Some uninfected children are not vaccinated because their parents do not consent. But the blame for the majority of the preventable disease in these young people rests not on the parents but on the local authorities, some of which either began the scheme late and developed it slowly or did not attempt it at all. In 1958 only 47% of all children aged 13 in England and Wales were tuberculin-tested and 37% vaccinated. If all had been tested the proportion vaccinated would have been about 79%; thus less than half the children who should be vaccinated were being vaccinated. It seems deplorable that the careful investigations of the Medical Research Council should not yet have convinced all local authorities that the children for whose health they are responsible can be protected from this serious disease, or that considerations other than medical ones should have prevented them carrying out the recommendations of the Ministry of Health. The Ministry, it appears, cannot force a local authority to use B.C.G. vaccine by the scheme they prescribe, yet at the same time they can prevent the vaccine being employed by local authorities in other schemes, even though the particular local circumstances warrant these. Thus, a child may be left unprotected either because the local authority will not provide vaccination within the authorised scheme, or because the Ministry will not approve vaccination out of the scheme.

The authorised scheme at present includes 13-year-old schoolchildren, and certain relatively small special categories at other ages.[14] Should the age of vaccination be reduced? Vaccination in the first few weeks of life could protect for an unknown period during infancy, and revaccination would be administratively easy in the early school years, but tuberculous infection of infants is declining rapidly, and it is unlikely that the great effort of attempting to vaccinate all infants throughout the country would be justified by the results. Moreover, the incidence of troublesome complications with the present intradermal route is higher in infants than in older children.[15] POLLOCK[16] discussed the advantage of reducing the age from 13 to 10. At this age fewer would already have been infected and more could be protected during the vulnerable years of adolescence. But, as he says,[17] "the tuberculin-positive proportion of the 13-year-old age group is diminishing each year . . . [and] the application of a mass vaccination scheme requires to be regularly reviewed as the epidemiological situation changes." SUTHERLAND suggests that a central bureau be established in connection with the official vaccination scheme. In this way changes in the tuberculin-sensitivity of children in different parts of the country could be observed and interpreted, and the notified cases of tuberculosis at later ages related to previous tuberculin sensitivity and vaccination. Such a scheme has been working successfully in Denmark for several years.[18] This central collection of information has much to commend it, and if the eradication of tuberculosis, and not just its "control", is the policy of the public-health authorities, it should not be administratively irksome. But its value would be reduced if the central authority did not have some power to compel local authorities to offer vaccination against tuberculosis. At the same time it might be profitable in planning national schemes to abandon the present rigid uniformity and to take into account major local differences in the risks of infection, even between parts of the same administrative unit.

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[13] Sutherland, I. *ibid.* p. 473.

[14] Ministry of Health circular 7/59.

[15] Gemmill, J. S. *Med. Offr*, 1959, 102, 141.

[16] Pollock, T. M. *Brit. med. J.* 1957, ii, [illegible]

[17] Pollock, T. M. *Tubercle, Lond.* 1959, 40, 379.

[18] Groth-Petersen, E., Knudsen, J., Wilbek, E. *Bull. Wld Hlth Org.* 1959, 21, 5.

Annotations

RABBITS

By the end of 1955 myxomatosis had destroyed over 90% of the rabbits in this country, but even as early as April of that year an attenuated strain of the virus caused extensive infection in Sherwood Forest Since then the less lethal form of the disease has been recognised in most counties of England and Wales, and many people have assumed that this is the natural course of events and that the infection can only persist in the less severe form In Australia Fenner[1] and his colleagues showed that the introduced lethal virus, which was different from our own, was soon replaced by less virulent strains and—which is more important—that after seven epizootics even the original virus killed only about a third of newly caught young wild rabbits In Australia attenuation of the virus thus appears to have favoured the natural selection of genetically resistant rabbits, and myxomatosis can no longer be regarded as of great value in pest-control So far as is known, no such selection has occurred here and British rabbits are no more resistant to the virus than they were before 1954

Differences in the evolution of the disease depend among other things on the complex relationships between virus, host, and vector, and in Australia mosquitoes (which Fenner has likened to flying pins) are the principal vectors Rabbits infected with less virulent virus will survive longer than those infected with a fully virulent strain more mosquitoes will therefore have a more durable source of virus provided that the nodular type of lesion of the attenuated strains remains rich in virus Under these circumstances natural selection will favour such strains, and indeed Fenner et al[2] showed that even when the highly virulent European strain was introduced on a large scale into an already infected area it dominated the peak of the epizootic during the summer but was supplanted by the local attenuated strains within a year Virus which is too attenuated may multiply so poorly that mosquito transmission is impossible, but such strains have not been isolated in the field

In Britain outbreaks of attenuated myxoma infection are probably still increasing, but there is no sign that these strains are supplanting the original lethal agent. According to Andrewes et al[3] evolutionary pressure here is more likely to favour fully virulent virus, partly, at least, because of the habits of the chief transmitter *Spilopsyllus cuniculi*, the rabbit flea Fleas will leave a dead animal and spread the infection, but they may not leave it at all or only when there is little virus available to contaminate the proboscis if the animal survives or has a long illness As Marshall and Fenner[4] point out this would, at least for a time, favour dissemination of fully virulent virus It is a platitude that infectious agents which kill all their hosts end by committing suicide, and possibly our present situation, where fully virulent and attenuated strains exist side by side, is a temporary evolutionary compromise How long it may continue no-one can predict, for much though Fenner and his colleagues have learned about the epidemiology of the Australian disease, we know much less here How the virus persists between outbreaks, and why and how it suddenly reappears in some districts after months or years of absence, we still do not know Possibly the discontinuity of the outbreaks in a population whose individuals have an average life-span of about a year will help to avert virus-resistance in rabbits Even if we escape the Australian epidemiological dilemma, we obviously cannot now count on an enzootic disease such as myxomatosis since it is both unpredictable and uncontrollable as a method of reducing our rapidly increasing numbers of rabbits There was severe damage to farm crops last year, and the activities of the rabbit clearance societies should be greatly increased and much more widely supported

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[1] Fenner, F *Brit med Bull* 1959, 15 240
[2] Fenner, F, Poole, W E, Marshall, I D, Dyce, A L *J Hyg, Camb* 1957, 55, 192
[3] Andrewes C H Thompson, H V, Mansi, W *Nature, Lond* 1959, 184, 1179
[4] Marshall, I D, Fenner, F *J Hyg, Camb* 1958, 56, 288

FLUORESCENT RED CELLS

Irradiated at a suitable wavelength, many substances of biochemical interest (porphyrins, stercobilin, certain vitamins, and chemotherapeutic agents, to name but a few) either fluoresce spontaneously or can be induced to do so by treatment with fluorescent material Others do not readily combine with these dyes, and a few actively extinguish their fluorescence That hæmoglobin belongs to this last category has been one reason why fluorescence microscopy has never attracted a following among hæmatologists Kosenow[1] outlined the scope of the method in the study of white cells, platelets, and the immature members of the erythrocyte series, but he agreed with earlier observers that the appearance of hæmoglobin in the cell blots out all morphological and chemical detail[2] Werth and others have shown that this transformation is due to active extinction by the hæm moiety of the hæmoglobin molecule[3] [4] Apart from occasional fluorocytes—cells which display brief red luminosity among the dark discs of ordinary red cells—the exceptions have been erythrocytes of patients with porphyria and lead poisoning

A year ago Donath and Lengyel,[5] of the Anatomical Institute of the University of Budapest, reported a series of experiments in which they had sought to overcome the fluorescence-extinguishing power of hæmoglobin without seriously damaging the red cells Using various chemicals (such as sodium hypophosphate) they found it comparatively easy to impart fluorescence to the red-cell stroma and thus partly to overcome the blackout effect of hæmoglobin, but neither by introducing such substances nor by altering the ionic state of the hæm iron could they influence the behaviour of hæmoglobin itself This they achieved, however, by treating red cells with hydrogen peroxide before staining or by applying the dye mixed with hydrogen peroxide erythrocytes could then be made to fluoresce vividly both on smears and in wet preparations

This work was taken up by investigators engaged in the study of possible variations in the hæmoglobin molecule in acquired disease Martos and her colleagues[6] found that fixed minimal quantities of fluorescent dye were necessary to induce fluorescence in hæmolysates of given concentrations, and, more surprisingly, that this fixed minimal quantity changed in chronic illnesses They now claim that such pathological states cause a structural change in hæmoglobin, and that this change can be detected by the altered capacity to extinguish fluorescence after hydrogen-peroxide treatment Similar changes were noted after X-irradiation [7] even after comparatively small doses, and before any other change in the blood-picture (such as lymphopenia), the blackout effect of hæmoglobin on the red cells became more resistant to attenuation by powerful oxidising agents

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[1] Kosenow, W Lebende Blutzellen im Fluoreszenz- und Phasenkontrastmikroskop Basle, 1956
[2] Wagner, K *Wien med Wschr* 1950 100, 808
[3] Werth, G *Acta hæmat* 1953 10 209
[4] Werth G, Eisenbrand, J *Z physiol Chem* 1955 299, 156
[5] Donáth, T, Lengyel I *Magyar orv Hetil* 1958, 99 930
[6] Martos, K, Geszti, O, Lengyel, I *ibid* 1959 100 973

These preliminary results still require a good deal of experimental support, and, once the experimental facts are established, they will have to be interpreted with caution (The data available at present do not even exclude the possibility that haptoglobulins were partly responsible for the changes described) Even at this early stage, however, the work reminds us that the genetically determined abnormalities of hæmoglobin are not necessarily the only ones, and that, impressive though the advances in hæmoglobin chemistry have been, important gaps still exist When we ascribe hæmoglobinopathies to minute chemical flaws in the globin moiety of hæmoglobin and dismiss the hæm moiety as normal, we should reflect that many of the clinical features (such as those resulting from changes in the oxygen-binding capacity) clearly point to altered function if not to altered structure of hæm Possibly in the experiments reported by the Hungarian workers the hydrogen peroxide led to chemical changes in the globin moiety of hæmoglobin which affected the fluorescence-extinguishing power of hæm The phenomenon could then be analogous in some respects to the change in the congenital hæmoglobinopathies it is certainly just as puzzling

INFANTILE STRUCTURAL SCOLIOSIS

AT one time diagnosis in orthopædics was followed almost automatically by treatment, usually for some gross deformity which needed correction Now, however, because orthopædic disorders are becoming less obvious and gross, knowledge of prognosis or the natural history of the condition is increasingly recognised as an essential preliminary to treatment Many orthopædic conditions are essentially self-curing, and accordingly complicated or expensive or potentially dangerous treatments are contraindicated Notable among such conditions are certain deformities of childhood in which time and growth are likely to correct the deformity—for example, most types of knock-knee and flat-feet, many deformities following fractures of the long bones, and even the gross deformities following an unreduced supracondylar fracture of the humerus

In 1936 Harrenstein [8] described what is now known as infantile scoliosis—that is, scoliosis appearing in early infancy without obvious cause and, in particular, without gross congenital bony anomalies such as wedged vertebræ or fused ribs In 1951 James [9] described 33 cases of infantile idiopathic scoliosis, and James et al [10] have lately described the natural course of the condition in 212 infants first seen below the age of three years In roughly a third (77) of these the scoliosis resolved spontaneously, in the remainder severe and progressive scoliosis developed In the early stages no bony abnormalities were detectable on radiographic investigation, and in 1 child, who died at the age of eleven months, no abnormality could be discovered on either macroscopic or microscopic examination It is still uncertain whether the resolving and progressive curves are basically the same at the beginning If they are, discovery of the cause of resolution might lead to an important advance in our knowledge of the ætiology and treatment of idiopathic scoliosis Meanwhile, there is much to be gained by further study of the natural history of severe deformities, and until this is understood it is wrong to claim that any particular treatment has been successful

SCHOOL PHOBIA

THE syndrome of " school phobia " was first described by Broadwin [1] in 1932, although the term was not coined until nine years later [2] It consists in persistent refusal to attend school, the child remaining at home with the full knowledge of his parents " Truants " behave differently, usually absenting themselves from both school and home Hersov [3] has shown that these two groups differ school refusers are more intelligent, of higher social class, work and behave better at school, are more timid, and have been less frequently separated from their mothers in early childhood The mothers are often over-protective and there is more neurosis in the family School phobics are afraid of separation from their mothers and homes, and Burns,[4] among others, has emphasised that it is this separation-anxiety rather than fear of school that is the underlying problem they are not phobic in the accepted sense, and perhaps, as Davidson [5] has suggested, they would be better called mother-philes than school-phobes—a term which casts an undeserved slur upon the pedagogues While school refusal is usually a symptom of a neurotic disturbance, truancy tends to be associated with delinquency

The number of cases seen in clinics is undoubtedly increasing both in America [6] and in this country [7], but Barber [8] has suggested that, in the Bristol area anyway, the increase reflects greater zeal on the part of school attendance officers, and the National Association for Mental Health after its two 1959 conferences on the subject said that it has no evidence of an overall rise [9] It is very likely that many children now treated as neurotic were previously dealt with as truants, or regarded as having some uncertain organic condition, for in such cases children present characteristically with somatic complaints, especially abdominal pain and nausea on school mornings

The treatment of early cases consists in firm support, and encouragement of mother and child towards a return to school Attempts to force the child only generate greater panic If this fails, psychotherapy, usually of both mother and child, may be required, but a compromise solution, such as allowing the mother to remain with the child at school, may bring about an early return Change of school in itself is useless, for it is not there that the trouble lies, but such a change does provide a fresh start and, in combination with other methods, may help Separation from the parents by residential schooling may be needed, but only after careful judgment and individual treatment, for in the obstinate case the child will immediately abscond Half of Hersov's group of severe cases

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7 Gesztı O Sztanyik L , Lengyel, I Martos K *Ibid* 1959, 100, 975
8 Harrenstein R J *Rev Orthop* 1936 23 289
9 James J I P *J Bone Jt Surg* 1951 33B 399
10 James J I P Lloyd Roberts G C , Pilcher M F *Ibid* 1959, 41B, 719

1 Broadwin, I T *Amer J Orthopsychiat* 1932 2 253
2 Johnson, A M , Falstein, E I , Szurek, S , Svendsen, M *Ibid* 1941 11, 702
3 Hersov, L M D Thesis Witwatersrand 1957
4 Burns C L C National Association for Mental Health proceedings of the 15th inter-clinic conference p 26 London 1959
5 Davidson S Address to Association for Child Psychology and Psychiatry, Dec 12 1959
6 Eisenberg L *Amer J Psychiat* 1958, 114, 712
7 Graham, J J *Times*, Nov 23, 1959
8 See *Lancet*, 1959, i 564
9 *Times* Nov 24, 1959

required inpatient treatment, but on the whole the outlook is good, especially for children below 11 years old of whom 89% attending one clinic were going to school regularly [10], over that age the figure dropped to 36% The "hard core" cases were found to come from the most seriously disturbed families in such cases the school refusal may well be a clinic refusal, and, later on, a work refusal [11] Clearly, the sooner treatment is started the better, and this requires efficient and rapid communication between parents, school, and the many other agencies that may become involved [12]

MEDIASTINAL MASSES

THE situation and radiographic appearance of mediastinal neoplasms, cysts, vascular abnormalities, and glandular enlargements sometimes give a clue to their nature, but short of thoracotomy an exact diagnosis is usually impossible Lyons et al,[13] reviewing a series of 782 mediastinal masses, urge that preliminary investigations additional to chest radiography should nevertheless not be neglected They found that barium swallow and angiocardiography not infrequently helped to establish the diagnosis or to assess operability, and scalene-node biopsy [14] above all proved to be a most valuable ancillary procedure Scalene-node biopsy established the diagnosis in 92% of lymphomas and in 72% of granulomatous lesions with otherwise negative findings, and was also the most fruitful line of investigation in metastatic mediastinal lesions Lyons et al emphasise that for full exploitation of the method technical experience is necessary a point also made by Aikens,[15] who reports useful results with this procedure in various respiratory conditions—especially sarcoidosis and, to a lesser degree, bronchial carcinoma In obscure mediastinal and pulmonary conditions it seems, therefore, that scalene-node biopsy may sometimes avert the necessity for thoracotomy

EXPLORING SUBCORTICAL FUNCTION

WHEN medically intractable epilepsy is to be treated by local cerebral surgery, definition of the precise site where the epileptic discharge originates is important Originally such operations were planned in relation to macroscopic abnormality of the cortex, but when the electrical substrate of epilepsy was recognised its location was assumed to indicate also the site of origin of the clinical seizure On this basis brain tissue showing such activity, even if macroscopically normal, was sometimes removed There is now increasing evidence that, although some relationship between the site of origin of electrical abnormality and epilepsy exists, the correlation is far from complete The search for a spike focus, and the excision of regions where it arises, are therefore now less keenly pursued—though the results are often beneficial

Earl Walker and his colleagues,[16] who have already contributed much to this subject, have reviewed the results of subcortical recording in temporal-lobe epilepsy They note that the absence of surface activity, including that from sphenoidal leads, does not exclude a subcortical temporal focus They also find that, as with surface activity, spontaneous subcortical spike discharges are often unaccompanied by any overt clinical attack and they suggest that these non-ictal discharges seem not to affect the normal functioning of the area, so far as simple tests of mentation can show

Stimulation of deep temporal-lobe structures and basal ganglia suggested that the threshold for excitation of amygdala and hippocampus is relatively low, and that spread of discharge from these areas is wide Confusion and alteration of thought were common, as were visceral, vasomotor, and emotional changes An interesting finding was that stimulation of amygdala, thalamus, and globus pallidus elicited pain in one half of the body The general picture is of visceral and affective responses from a number of sites, including medial temporal, inferior frontal, and thalamic But relatively few stimulations, even of those producing electrical after-discharge, gave rise to clinical features of any sort

INFECTION AT THE HAIRDRESSER'S

MOST men choose their hairdresser for reasons of nearness, cheapness, or cleanliness (Women add other criteria less easily summarised) The "cleanliness" is judged, we would guess, by standards that are basically unconnected with health People dislike the shop which is stuffy or which has a smell to which they are not accustomed They do not care for a floor littered with shorn locks, or sheets which have not been laundered recently With shame they may admit that they avoid the shop whose customers come from another income group (whereas they would share a seat on the omnibus without a thought) They seem to feel that they may "catch something" Yet the evidence that the hairdresser's shop plays any important part in the spread of disease is negligible "Barber's rash" is primarily an eczema, often complicated by staphylococcal infection, and though it can be spread by the use of a common razor or towel, the bacteria more often come from the patient's own nose Moreover, public shaving is a dying custom and many of those who have this disease have never been shaved *Microsporon audouini* was certainly disseminated by the hairdresser, but ringworm due to this fungus is now rare compared with that derived from animals (That it was commoner in boys than girls may have been due to the fact that small girls tended to have their hair cut at home and the close crop of the small boy allowed the fungus easier access to the skin) Any ill-ventilated enclosure encourages the spread of respiratory infections, but the barber's shop cannot be more dangerous than the four-ale bar

An attempt to give some objective value to the assessment of cleanliness in hairdressers' shops has been made in Glasgow [1] Fifty establishments were subjected to thorough inspection and judged by much the same standards as those used for eating-houses, with particular attention to such things as the disinfection of instruments As might be expected, there was wide variation between the shops indeed, almost the only thing they had in common was poor sanitary facilities for the staff Shops patronised entirely by women were on the whole cleaner than those reserved for men, but this is not surprising in every walk of life men wear dirtier clothes and have dirtier habits Many bacteriological examinations of premises and equipment were made, but the difficulty here is that, to be really useful, numerical values must be compared with other numerical values, and one would like to know how the microflora of the hairdresser's shop compares with that of the railway carriage or the doctor's waiting-room The failure to recover ringworm fungi was interesting and encouraging but likewise evokes a further question how common was the disease in Glasgow at the time?

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[10] Rodriguez, A, Rodriguez, M, Eisenberg, L *Amer J Psychiat* 1959, 116, 540

[11] Warren, W Cited by L Hersov (footnote 3)

[12] *Med Offr*, 1959, 102, 292

[13] Lyons H A., Calvy, G L., Sammons, B P *Ann intern Med* 1959, 51, 897

[14] Daniels, A C *Dis Chest*, 1949, 16, 360

[15] Aikens R L *Canad med Ass J* 1959, 81, 891

[16] Lichtenstein R S, Marshal, C, Walker, A E *A.M.A Arch Neurol* 1959, 1, 288

[1] Wilson, T S, Carter H S *Med Offr* 1959, 102, 249

Fastidiousness is generally an aid to hygiene, and people who normally prefer to keep to their own brushes and towels are entitled to demand a high standard of cleanliness in places where such things serve a succession of customers They will therefore welcome the medical attention to these matters which this investigation shows Nevertheless the general notion that hair is rather dirty stuff is now largely irrational, dating perhaps from the days when it nearly always *was* rather dirty On bacteriological examination, clean hair shows few bacteria in it and even fewer that are likely to cause disease

TEAMWORK FOR CLEFT PALATES

THE management of babies with cleft palate has rightly become the concern of a team rather than an individual This enlightened approach, which has been particularly evident in Britain, was demonstrated during the L D S centenary celebrations last July by the choice of subject for the main scientific symposium—namely, Treatment of the Cleft Palate [1] An embryologist, a plastic surgeon, an orthodontist, and an expert in prosthetics outlined an integrated attack in which none could succeed alone No claims for any startling technical advance were made, though some discussion centred on the scope of the early "orthopædic" treatment advocated five years ago by McNeil [2] On this issue one point is clear that no intraoral appliance in early infancy (or later) can conceivably achieve closure of the soft palate—and therefore the operative repair of this vital structure cannot be obviated It was emphasised that patients must be considered as people—"this lesion is a fissure in the palate completely surrounded by a human being" It was imperative that they should not be allowed to reach adult life as vocal, cosmetic, or dental cripples

The surgeon should at the first opportunity give the parents, who may be appalled by their child's deformity, an honest but reassuring outline of the therapeutic plan Two-thirds of palatal clefts are "complete", involving lip and alveolus, and the stages in these severe cases can broadly be summarised as follows repair of the lip and nasal floor is carried out at 3 months, and repair of the hard and soft palate at 18–24 months, orthodontic supervision (which should be begun soon after birth) can reach the stage of maxillary expansion at 4–6 years, speech therapy (if indicated) should also be begun at about this age, but in a good home this task may be supererogatory Prosthetic treatment often consists in merely replacing an absent lateral incisor, but a few surgical disasters are still seen, and for these (as for the rare cases where primary surgery is impossible) an obturator may sometimes prove startlingly effective in providing clear speech Finally, secondary surgical adjustments to lip, septum, and nose may be indicated and are usually deferred until the patient is 15 or older

At the symposium an issue of particular importance was raised—the operative mortality and its possible relation to the patient's age Strong claims have been made that the palate should be repaired at the first birthday, and in a *recently published series* [3] the subsequent operative mortality was 3 7% This is at striking variance with the figure given by Fogh Andersen (cited in the same paper), who operated at about the 2nd birthday with a death-rate of 0 6% This comparison offers up-to-date evidence for the view, held in earlier days, that a young baby is not as a rule an acceptable risk for this major procedure While the hazards have been enormously reduced, *particularly* by *modern* standards of anæsthesia and general management, they have not yet been eliminated In the opinion of many experienced surgeons sound reasons still exist for deferring operation until the deciduous dentition is complete—and there may be special considerations which justify postponing operation for 3 or 4 years Contrary arguments, based on theories of the developing patterns of speech, carry little weight when set against the cost in lives Perfect speech is an admirable goal, but the death of a child once in every thirty operations is a heavy price As the published results of *Fraser and McCredie*,[4] Davies and Danks,[5] and others have shown, the death rate ought not to exceed 0 5%—and "should be nil"

DIAGNOSIS OF MULTIPLE PREGNANCIES

AN interesting report on the use of the electroencephalogram in the diagnosis of multiple pregnancy by identification of *fœtal cardiac activity* has appeared in the United States Using a standard eight-channel Grass model III electroencephalograph, Novotny et al [6] studied 321 tracings from 295 patients They found that the 28th to 36th week *of pregnancy* was the most difficult time for demonstrating fœtal heart activity, the best results being obtained between the 20th and the 28th week In 81% of cases single or multiple pregnancy was *correctly diagnosed*, or fœtal death confirmed, and in the 20th to 28th weeks the proportion was 90% Difficulties were encountered as a result of excessive maternal muscle artefact, excessive fœtal *activity*, poor cooperation by the patient, failure to empty the bladder, or maternal tachycardia Accordingly 20 tracings were technically unsatisfactory for interpretation, while *in* 39 others either the *fœtal heart activity* was *not* demonstrated although the fœtus was alive or only one heart was revealed when two or more fœtuses were present

As an alternative to the positive demonstration of *multiple pregnancy* by X-rays, this method cannot yet be accepted completely Because of the dangers to the undiagnosed second twin during delivery, the *method of* diagnosis should be thoroughly reliable, *and the likelihood* of error with the electroencephalographic method is not outweighed by the very early diagnosis which may be possible (twins were correctly diagnosed *at 16 weeks* and triplets at 20 weeks, while *an* X-ray at 21 weeks in the same case of triplets was still inconclusive) The great advantage of this method lies in the avoidance of radiation hazards, and if further experience were to increase its accuracy it might prove a valuable additional means of investigation

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SIR JAMES PATERSON ROSS is to succeed Sir Francis Fraser as director of the British Postgraduate Medical Federation when he retires on Oct 1

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1 *Ann R Coll Surg Engl* 1959 25 225
2 McNeil C K Oral and Facial Deformity London 1951
3 Reidy J P *Brit J plast Surg* 1959 12 215
4 Fraser I, McCredie, J A *Brit med J* 1955 ii 667
5 Davies R M, Danks S *Anæsthesia* 1953 8 275 See *Lancet* 19[illegible] 239
6 Novotny, C A, Hass W K Callaghan D A *J Amer med Ass* 19[illegible] 171, 880

Special Articles

THE MARRIED MENTAL DEFECTIVE

A FOLLOW-UP STUDY

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EVEN before the Royal Commission's report, public opinion was fast moving away from the ideas current at the beginning of this century when mental-deficiency legislation was being formulated. Though prohibition of marriage was dropped from the original Bill, under the Mental Deficiency Act of 1913 many mental defectives were segregated in colonies for the years when they were most likely to bear children. As recently as 1949 the Ministry of Health expressed the opinion that mental defectives were generally unfit for the responsibility of marriage and of parenthood, and that, even if they were able to conform to normal social requirements in sheltered conditions in the community, they were rarely able to stand the strain of bringing up children and managing a household.

Today some well-informed people are undoubtedly seriously disturbed by the possible social and genetic consequences of community care. Detailed studies of intelligence levels among the children of mental defectives are conflicting (Penrose 1938, Brandon 1957). Little attention has been paid to the social performance of families in the community, though several follow-up inquiries (Ainsworth et al. 1945, Mickelson 1947, Hartzler 1953, Wolfson 1956) throw some light on the American scene. The object of the present investigation was to choose a random sample of the married defectives in Sheffield and follow them up systematically to see what success they had made of marriage.

METHOD

We selected the cases by going through the departmental records of all mental defectives ascertained since 1915. Of the 2877 records scrutinised 640 referred to patients in mental-deficiency hospitals, and 1293 to mental defectives under statutory supervision. The remaining 944 had been discharged from statutory supervision. Defectives are usually discharged from statutory supervision when they have shown themselves capable of leading a stable life within the community.

Marriages listed for investigation were those recorded on the case-notes. These numbered 120 men and 122 women, including ten instances in which ascertained defectives had married each other. Other marriages may have occurred after discharge from supervision, but we investigated only those given in the case-notes.

THE SPOUSES

Of the original 242 defectives 45 (19%) are untraced. 19 of those untraced are known to have moved from Sheffield, though some may have returned unknown to the department. No attempt was made to follow up any patient outside the city boundary, because there is a danger of rediscovering the less satisfactory families and overlooking those who have merged successfully in the community. Searching for families through intermediary authorities adds a further element of uncertainty as to whether the people traced are representative of those originally selected. Eventually 197 (81%) people were traced. Of these 98 were still under statutory supervision (including 13 in institutions) while 99 had been discharged. An inquiry was made and a pro-forma completed by the district health visitor or mental welfare officer on the basis of an interview or from previous knowledge. Opinions have occasionally been modified in the light of further information from other departments or from voluntary bodies.

Intelligence level

The intelligence quotient of 122 of the defectives in the survey was recorded. In 93 (76%) the I.Q. distribution lay between fifty and sixty-nine, 13 (11%) were above this range and 16 (13%) below. There were proportionately more men with I.Q.s over sixty-five, probably because they were ascertained as mental defectives on account of behaviour difficulties at school or other indiscretions, despite a moderate level of intelligence.

Size of Family

The mean age of marriage among the men was 22.2 years compared with 25.2 years among the women defectives. In the country as a whole men marry 3 years later than women. Live births, however, were 50% greater than the norm for women married at the same age and for the same length of time. The birth-rate was also appreciably above that in families of unskilled workers (Registrar General 1959).

Infant Mortality

Information about infant deaths was often incomplete and infant mortality has only been assessed since July, 1944. Nevertheless 26 infants are known to have died, equivalent to an infant-mortality rate of about 73 per 1000 live births. This is in line with earlier findings (Departmental Committee on Sterilisation 1934, Juda 1934).

Employment

Of the mentally defective husbands 34 were in unskilled occupations but 24 were doing semiskilled or possibly even skilled work. There was not enough information to classify the employment of 13. 5 husbands were temporarily unemployed, 13 were chronically unemployed, 6 were in mental-deficiency hospitals, and 5 were in prison (i.e., 29% were not in employment). Of the mentally defective wives only 14 were employed outside the home.

9 of the men were registered as disabled persons, and of these 4 were unemployed. 2 others, who were among the chronically unemployed, were on the blind register.

Criminal Record

5 husbands were serving a prison sentence and a further 7 had served previous terms of imprisonment. The offences included robbery with violence (1), larceny (4), child neglect (2). Another 30 had been before the courts for stealing, sexual offences, or minor misdemeanours. 11 of the mentally defective wives had appeared before the courts for offences such as prostitution and theft but only 1 had served a prison sentence.

Broken Marriages

38 divorces or permanent separations were met in the survey, equivalent to 20% of the total families traced. 9 marriages were obviously unsatisfactory even to the outsider. Nevertheless most of the marriages seemed to be reasonably happy and stable even when the families presented problems to others.

Child Care

34 families were known to the National Society for the Prevention of Cruelty to Children, and the children's department had been concerned with a further 11 families over reports of neglect or other circumstances that led to the children being placed in the care of the local authority for several months or longer. These 45 families were almost a third of the families who had one or more children—a disturbingly high proportion. According to departmental records the childhood background of the defective parent was considered unsatisfactory in 28 of 41 neglected families (68%) compared with 56 of the remaining 126 families (44%).

THE SECOND GENERATION

Of the 377 children 46 were unsuitable for education in an ordinary school, or were so retarded that it was unlikely that they would prove suitable This is equivalent to 10 6% of live births or 12 2% of children surviving the first year of life

6 children were in mental-deficiency hospitals, 26 were in special (E S N) schools, 9 were at occupation centres, 5 were retarded children under school-age We saw all the pre-school children personally and carried out an intelligence test where possible

Many head teachers are very tolerant of backward children and it seemed that there might be other retarded children from the survey families whose names were not put forward for transfer to a special school Evidence is available from the results of routine group intelligence tests given at ordinary schools as part of the secondary selection procedure Records were traced of 57 (76%) of these children in the survey families 59% of the test scores fell between eighty and one hundred, 12% were above this range and 29% below Only 3 children had scored under seventy in both of two I Q tests, which suggests that few mentally retarded children had been overlooked

Among the survey group 11 6% of schoolchildren were attending special (E S N) schools, this percentage is about 17 times higher than for the Sheffield school population as a whole The proportion of children of compulsory school-age who had been reported as ineducable (5 6%) was also 17 times higher Of the 23 survey children attending a special school for the educationally subnormal, only 2 had an I Q above seventy (Terman-Merrill)

SUCCESSFUL AND LESS SUCCESSFUL

26 families could be described as problem families in the sense that they had presented problems to several departments of the corporation and to other social agencies The home environment seriously jeopardised the mental and physical development of the children In 15 (58%) one or more children had to be removed from the care of the parents, though the family was not necessarily split up at the time of the survey Several other families undoubtedly would have fallen into the category of " problem family " but for the fact that at the time of the survey the parents had separated and the family had ceased to exist as an entity Of 10 families where both man and wife had been ascertained defectives 5 were regarded as problem families of the other 5 marriages only 2 could be considered satisfactory, 1 of these being a childless couple

40 families out of 90 (44%) where the man was defective and 38 families out of 87 (44%) where the woman was defective seemed to be living reasonably happy and normal lives They were self-supporting within the community and not a special problem to any social service Many families in the survey showed unsatisfactory features such as poor child care, slovenliness, or obvious signs of marital disharmony Sheridan (1956) has observed that temperamentally stable mentally defective mothers can cope with their households fairly well while they have only one or two children, but when their family responsibilities outgrow their capacity they become overwhelmed Our own experience supports this view Excluding the 38 marriages where the husband and wife had separated, there were 92 marriages childless or with one or two children, and 57 marriages with three children or more Of the small families 59 (64%) appeared to be quite successful from the point of view of social adaptation, whereas among the larger families only 22 (39%) were satisfactory Of the 15 families where husband or wife had an I Q of under fifty only 2 were in the satisfactory group, and there was reason to doubt the validity of their I Q assessment

Discussion

The picture that emerges is not clear-cut Young people of low ability are destined either for success or failure, and, if only there were some sure method of differentiation, it would be easy for the community to arrange for a psychiatric assessment and help them in a rational manner In fact, however, this is far from possible Some of those with the most depressing record suddenly achieve stability, and settle down in a way that is a credit to them With I Q s of fifty or above there seems no close correlation between intelligence level and social adaptability, though we doubt whether a mother with an I Q of under fifty five or so is really mentally capable of raising a family satisfactorily Even here, however, where there is only one, or possibly two, children, the standard of care may be adequate The impression of the visitors was that mental defectives tend to choose, or be chosen by, a partner of about their own intelligence level Undoubtedly, however, that little extra ability, if it is there, can make all the difference in enabling a family to manage its affairs in a way acceptable to the community

Though families exist where all members are obviously mentally subnormal, usually they tend to show ranges of ability not so very different from the average The size of the families is larger than the average, though the additional births are to some extent balanced by the number of infant deaths The employment record of the defectives was fairly good, despite a hard core who contributed little or nothing to the support of themselves or their families The proportion of men who had fallen foul of the police was rather high Most had been dealt with under the normal penal procedure, though 13 appear to have been admitted to an institution as a direct result of the offence In the survey a fairly high proportion of the children found neglected were the offspring of defective parents who themselves had an unsatisfactory upbringing

The reasons why some families have failed may appear only too clear, but an explanation of the successes must take account of social adaptability and tolerance Similarly, the community must be tolerant and adaptable However comprehensive the mental health services, there will always be those who do not conform to recognised codes of behaviour Patience and forbearance will be necessary if the mentally handicapped are to live within the community in peaceful coexistence

This follow-up study could not have been carried out without the health visitors and mental welfare officers who undertook the field work Much confidential information has been provided by social agencies and by other departments of the local authority, but the opinions expressed are our own and do not necessarily reflect the views of the agencies consulted or the Sheffield City Council

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THE AMERICAN SCENE

SOME striking facts about medical developments in the Jnited States are given by Dr WILLARD C RAPPLEYE n his report on Dec 1 as president of the Josiah Macy, r , Foundation[1]

upport for Research

He begins by speaking of the " enormous expansion of esearch funds now available from governmental and ther sources " For the National Institutes of Health at 3ethesda, the U S Congress voted about 400 million lollars, or nearly 50 million dollars more than the institutes asked for In authorising this increase of 36% over he previous year's expenditure President Eisenhower xpressed concern lest it should actually " lower the quality f the projects supported ", divert into research too much f the man-power and other resources needed for ' equally vital teaching and medical practice ", or make nedical research and training more dependent on federal unds But large sums are at present collected by voluntary agencies for example, last year the American Cancer Society raised nearly 30 million dollars, the National Tuberculosis Association nearly 26 million, the American Heart Association over 22 million With smaller incomes, the Muscular Dystrophy Association raised nearly $5^{1}/_{2}$ million dollars, the National Association for Mental Health 5 million, and the Arthritis and Rheumatism Foundation 3 million

Dr Rappleye refers to the way in which the control, direction, and utilisation of research-workers is being detached from the educational institutions, so that many investigators are becoming " journeymen scientists ", often with little or no responsibility for teaching or institutional services

> " Comments are increasing regarding the large numbers of young scientists who are employed on short term research or traineeship funds whose future livelihoods and careers are uncertain. Hundreds of these young men and women are becoming worried about their futures which is being reflected in reluctance of others to enter the field so largely dependent on governmental, foundation, industrial or other impermanent funds "

Medical Education

The amount of money spent on medical education represents only 1% of the total expenditure for health services (and it includes numerous hospital services which should partly be supported from non-educational sources)

> " One fortieth of one per cent of corporate profits of American industry before taxes would be sufficient to cover the teaching deficits of the 85 medical schools Private practice and medical insurance fees are helping in a number of instances to maintain the clinical staff More financial support from various sources is urgently needed if the obligations of medical education as the essential feature of an adequate health service of the nation are to be maintained."

Though usually the university is regarded as responsible for the preparation of doctors, a substantial part of the clinical education of medical students is often provided in non-university hospitals Moreover, over three-quarters of the 12,469 approved internships and over half the 31,818 residencies are in such hospitals

> " Fortunately, many of the non-university hospitals now have modern laboratory and other facilities and professional staffs of excellence and good training, some of them on a full-time basis, who would be able to give a high quality of instruction to medical students, to house staffs and local practicing physicians if given the opportunity and incentive A large reservoir of potential training opportunities exists which might be utilized through proper educational leadership and guidance "

" In view of the avalanche of new knowledge and the masking of scientific developments in part behind commercial exploitation the problems of keeping a physician in practice up-to-date presents a major challenge to the profession, hospitals and medical schools " New and vigorous plans for postgraduate education must be made if the public are to get the benefit of scientific advances This Dr Rappleye describes as a " crucial aspect of modern medical care " Writing of the possible incentives to practitioners to continue their education, he says that " the idea of a periodic re-examination of physicians is again under review "

Meanwhile there is the still growing problem of absorbing graduates of foreign medical schools last year there were 9254 foreign-trained interns and residents in 821 hospitals

> A quarter of these were in New York, where " in the municipal hospital system eleven of the institutions have not a single graduate of an American school " Most of the foreign group in New York City come from the Philippines (1598), Turkey (587), and Mexico (500) There are now about 2200 Americans studying medicine abroad—usually because they cannot get into an American school Yet " some of our own institutions have not enough acceptable applicants to fill their classes, sometimes because of geographical restrictions on students in certain state medical schools "

The Surgeon General's Consultant Group on Medical Education has recommended an increase in the annual output of American medical schools by 3600 (at present it is about 6800), and has proposed the creation of 20–24 new schools

Prepayment for Illness

Discussing the continuing difficulties of the Blue Cross and Blue Shield schemes under which so many Americans insure against illness, Dr Rappleye says

> " The challenge immediately ahead is the extent to which premiums on a voluntary basis can meet the costs of expanding hospital services There is some evidence to indicate that the premium income on a voluntary basis is not likely to rise much above one-third of the total costs of hospital care in the aggregate That this figure may be somewhere near correct is illustrated by the recent decision of Canada to provide complete hospital service for the entire population on the basis of a $33^{1}/_{3}$ per cent contribution from the individual through pay-roll deductions or other devices It is of interest that Austria has just adopted the same formula."

Proposals have recently been made by the labour unions of New York to organise their own chain of hospitals and medical services, and the New York County Medical Society has offered to cooperate in such a plan In Detroit a Community Health Association, sponsored by the United Automobile Workers Union, will shortly be launched The American Federation of Labour/Congress of Industrial Organisations are now in favour of grants to medical and dental schools not only for equipment and plant but in defraying operating costs " They continue to recommend the pre-payment plans for consumer-controlled health service plans

" Younging " of the Population

A new set of problems, Dr Rappleye says, is confronting the country and medical services through the " younging " as distinguished from the " ageing " of the population The number of people under 20 years of age will reach 90 million, or 40% of the population, by 1970

> " An interesting prediction is that by 1970 those of 65 years of age or older (roughly 21,000,000) and those below 20 years

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[1] The Foundation's address is 16 West 36th Street, New York 36

of age (roughly 90,000,000) will represent over 50 per cent of the entire population of the country It is obvious that those between the ages of 20 and 65 will be bearing over one-half the economic and certain other responsibilities of the nation "

Medicine and the Law

Delusions or Cruelty?

A HUSBAND petitioned for divorce on the ground of his wife's cruelty The essence of his case was that from 1954 onwards the wife persistently made false and baseless accusations against him that he was carrying on with other women, and had nagged him on this theme incessantly, for hours at a time

Early in 1955 the wife, who was then about 35 years of age, was seen by Dr J G Hamilton, consultant psychiatrist at the Bethlem Royal Hospital On March 12, 1955, the wife was admitted to that hospital, and remained there until May 28, 1955 She then returned to live with the husband She soon renewed her accusations, suggesting that her husband had been carrying on with other women while she was in hospital In October, 1955, she was again seen by Dr Hamilton She then admitted that some of her accusations against her husband were false, and that she knew they were false when she made them She said that some of the things she had said to her husband had been said in order to trick him

Dr Hamilton gave evidence that, in his opinion, the wife was paranoic, and suffered from delusions, she was never certified and he thought it was improbable that she was ever certifiable He said that she sincerely believed that her husband had affairs with other women, and, despite the fact that she had admitted that some of her accusations were untrue—which was exceptional in such cases—he did not consider that that was enough to outweigh the other reasons for saying that she was deluded When she made these accusations against her husband, she knew the nature and quality of her acts, in that she knew she was accusing her husband of unfaithfulness, but she did not know that what she did was wrong Indeed, she believed that what she did was right She felt that she was a wronged person who had a great grievance and that it was proper for her, believing that her husband was being unfaithful to her, to say so and to act as she did The wife crosspetitioned on the ground of cruelty

Mr Justice **PHILLIMORE** said that with regard to the husband's charge of cruelty and the answer which had been put forward, there was a presumption that a person was sane so as to be legally responsible for his or her acts The burden of proof was on the wife to prove that, by reason of her state of mind, she either did not know what she was doing or did not know that she was doing what was wrong If she discharged that burden of proof, she could not be held guilty of cruelty It was quite possible that in the autumn of 1954 and, indeed, until her discharge from hospital in May, 1955, she did not know that in making these charges against her husband she was doing what was wrong When, however, she recanted, and admitted that she knew that some of her accusations were false and that some of the things she had said had been said with the object of tricking her husband, it was impossible to hold that thereafter she was not legally responsible for her conduct Her continued accusations therefore amounted to legal cruelty The husband was accordingly granted a decree *nisi* As the wife had also made out her crosscharge of cruelty against the husband, she, too, was granted a decree *nisi*

Pethers v Pethers & Wolff—*Probate Divorce & Admiralty Division* Phillimore J Jan 18 1960 Counsel and solicitors Miss M Morgan Gibbon and Trevor Guest (Copley Singleton & Billson), *Dudley Collard* (Jaques & Co), Leonard Pearl (Walford & Co)

D R. ELLISON
Barrister at-Law

In England Now

A Running Commentary by Peripatetic Correspondents

I BELIEVE I have at last found a valid use for the drug firm circulars on antibiotics To make my point I must describe a scene which is continuously repeated throughout the country

Seven of us are seated in the board-room of the Peripheral Regional Hospital Board to select the best candidate for the post of consultant omphalologist to the Central Group of Hospitals We have seen six excellent candidates, all with the correct qualifications (M D , M R C P , F F O), each at an appropriate stage in his career Dr F has been eliminated at the first round because he made an ass of himself at interview he had not only failed to visit the hospitals, he was also completely unaware that the professor on the committee had written a monograph on omphalomancy

The chairman now goes round the table for the second time, asking for two names, please, in order of preference It is immediately clear that we are going to have a long session, for there are three first votes for Dr A and three for Dr B This, mind you, is hardly surprising Dr A —the local boy, no genius but a sound chap—has collected the first votes of the three local members Dr B —the bright boy from the metropolis, with strings of publications and eulogistic references from Harley Street—has the votes of the three others The Chairman has not revealed his hand The pro-A faction ("We cannot be sure that this man B would fit in with local conditions ") is adamant, and the pro-B element ("Our job, Mr Chairman, is to appoint the best man ") is equally immovable The argument is becoming heated it looks like an impasse

It is suddenly noticed, however, that all six second votes have gone to Dr C , who is neither metropolitan nor local, who has spent half his time in teaching hospitals and half in regional hospitals, who has a wife and two children, who has written just three articles, and who has a pleasant personality "I liked that man," says the Chairman, "I thought he interviewed well " The factions dissolve, all agree to support Dr C He is brought in and, somewhat to his surprise, offered the job In point of fact—and less surprisingly—he will do it very well

The moral? Clearly, Dr C has shown "broad-spectrum acceptability " Dr A and Dr B should have spent more time over breakfast, reading the literature instead of just sorting out the blotters

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Unlike another peripatetic correspondent, I have never felt so close to my dustmen as all that Indeed, it wasn't until it cropped up in the public-health course that I realised how this particular face (of Britain, I mean, not the dustman) was changing Now not only have our City Fathers equipped themselves with end-loading gravity-packers, but so have the R D C. down the road But, however much they may enchant the kids (and me) by sticking their tails up in the air, I still can't see how they're emptied Do they stand on their heads or their tails, or are the contents so densely packed that some unfortunate dustman—perhaps dignified by the status of "disimpactor "—has to dig it all out with a shovel?

• • •

In Service medicine you meet some interesting symptom-complexes in the different age-groups

The *under-twenties*, with a string of symptoms, any two of which are incompatible with life, linked with rosy cheeks a horse-like appetite, football twice a week, and dancing every third night till 3 A M , present the unusual combination of desperate illness in a healthy body Unaccustomed to sickness the mild symptoms of a cold are resented as a gross departure from normal The giddiness induced by a slight pyrexia is regarded as impending dissolution and the dysphagia of swollen tonsils as acute diphtheria or worse This age-group is highly suspicious of older men (of from 21 up), and we must view their symptoms in the same grave light as they do

The *twenties to twenty-fives* form an interesting subgroup The main morbidity here is love, Yogi, surrealism, and a desire to get away from it all The mortality is nil and they improve amazingly in the warmer summer weather Consultations in this group are somewhat one-sided as the patient does most of the talking

The *twenty-fives to thirties* are connoisseurs of trivia The slight distemper in the temple following guest night is not looked on as divine retribution, but as an early sign of brain tumour which should be investigated at Queen Square at once The slight metatarsal ache following the tango, " but never the foxtrot doctor ", is expected to bring a posse of leading London orthopods at a sharp trot

For those from *thirty upwards* any form of sickness is out of the question. The subject with a wife, children, a house, insurance, and a car (none of which he can afford) is only concerned with the struggle for survival Surgery must, as it were, be done on the run, and he is only brought to his knees by some catastrophe like mesenteric gangrene

* * *

Since I left the National Health Service and joined the medical department of a large pharmaceutical organisation, I have had many opportunities to compare and contrast these two ways of life

For a start, it is a great relief to find that I am no longer part of the registrar problem, and I hope that the world of commerce will prove less uncertain for me than the clinical rat race

The material benefits are obvious The work is light and most remunerative Until the past few months I had not had regular Saturday mornings off since I went to kindergarten at the age of five, and to have every Saturday morning to myself is indescribable luxury I no longer find that medical emergencies clash with social engagements, though, perhaps surprisingly, my plans still often have to be altered, for the business executive always changes all his arrangements at least once, at the last moment

It is a pleasure to eat and drink in the style to which one would like to be accustomed, and memories of dreary and monotonous hospital food are soon forgotten as one becomes used to excellent and leisurely meals eaten in the company's interest, and at its expense

I have a large and reasonably quiet office, and a private secretary who works for me alone, instead of part share in an overworked, underpaid, though invariably good-tempered and efficient, medical secretary

I had expected to find the efficiency of commerce a change from the National Health Service's maladministration, but in this context my old and new jobs are strictly comparable I really believe that in business there is more of penny-wisdom and pound (or thousand-pound)-foolishness, than in the N H S itself

There remains only one thing to add—the work is extremely interesting, perhaps even useful, and has rather less routine in it than any other job I have done

Incidentally, in spite of all this plushiness, we are still served, at four in the afternoon and eleven in the morning, with the same terrible tea and appalling coffee

* * *

She was a farmer's wife from the Fens, accustomed to good food and good living, and very free to express her thanks in the medium she knew best Fortunately when she developed secondaries from breast cancer they responded to hormone therapy Stilbœstrol did the trick and the years seemed to roll away as she lost her pain and regained her vitality Being a mere male I naturally took the deluge of eggs which she presented to me as a tribute to the profession Perhaps I should have known better

The sad day came when stilbœstrol lost its magic. In despair I turned to testosterone The pain went but so did the harvest of eggs I found that Sister was getting them

Letters to the Editor

CASUALTIES AND CASUALS

SIR,—The work underlying Dr Fry's article of Jan 16 prompts me to express warm approval As chairman of a committee planning a new teaching hospital I have noticed more than once the different interpretations which various members of my committee place upon the word " casualty " Some come to their first consideration of the planning of a hospital casualty department with memories of casualty-clearing stations, casualty lists, and the like In fact they conform with Dr Fry's observation that the word " casualty " implies " an accident or a serious or fatal event " In an attempt to clarify this semantic confusion I have described a hospital casualty department as an " accident and emergency department " An intractable epistaxis occurring when the family doctor is on his round and unavailable, an attack of renal colic when at work, a foreign body lodged in a small child's nose or ear, or a generalised convulsion in a child *is* an emergency from the patient's or parent's point of view, and no reclassification by doctors or administrators will prevent such cases presenting themselves with a sense of urgency at the hospital The fact that their National Health Service family doctor might, if available, in many instances be able to deal with the situation does not detract from that sense of urgency In any discussion of this subject agreement on this point is fundamental If we are not to receive them in casualty in future what are we to do?

One alternative, as Dr Fry seems to suggest in his discussion, is that some sort of selection of cases should be enforced But by whom? Not by the porter on the door, surely only by the casualty officer, and that is what is happening now

The issue is perhaps only confused when Dr Fry writes " agreement has not yet been reached on the part that the casualty department should play ", and three lines (and one sentence) later " In my own series only 60% of cases were ' casualty ' problems " Does he mean that only 60% were cases of " accident or a serious or fatal event ", or does he mean that only 60% were found, after careful examination by the casualty officer, to fit in to his present idea of what a casualty department should cater for? And anyway why " *only* 60% "? The figure is an index of the patients' diagnostic ability of their own urgent troubles and seems to me to be pretty good I wish I could believe I could be 60% right in such circumstances

From the medico-administrative or planning aspect of the casualty department of the future, three factors seem to be important but may be difficult to assess

First, whether in any given neighbourhood the total number and rough distribution among diagnoses, ages, and sexes is likely to alter significantly Dr Fry's record of nearly double the number of new patients in 1958 as compared with 1946 is of interest here

Secondly, whether the trend of any such change warrants a change in the selection of the persons (the consultants) in ultimate charge of casualty departments For instance, would an orthopædic surgeon be peculiarly appropriate to deal with Dr Fry's series of 2935 new patients in which 272 (9%) were fractures The remainder (91%), we should notice included sepsis, poisonings, various medical problems, soft-tissue trauma, burns, psychiatric problems, &c.

Third, whether we can anticipate any change in the pattern of general practice (group practice, health centres) which will cater for the 30% of cases immediately discharged and the 11% referred to their general practitioner

I think that we need not agree with Dr Fry that " the present-day casualty department has no specific function " The patients who, as taxpayers, own it and pay for it evidently think it has If we disagree with them and agree with Dr Fry that the department is misused or abused it is up to us to suggest a remedy Dr Fry is probably wise to exclude such suggestions from his article

In analysing the " referment " of these cases Dr Fry raised another cogent point Should a casualty department confine itself to first-aid and sorting? There are figures showing the distribution of the arrival of casualties over the 24 hours and from a study of these we have concluded that if the personnel is to be sufficient to cope really promptly and effectively with the " peaks " of accidents and " genuine " emergencies, there will be many idle hands in the department if no appointments for 2nd and 3rd attendances are given in the casualty department, if, in other words, referral is 100%

It would seem sensible to re-define our casualty departments as " accident, emergency, and dressing-stations " and plan along these lines

We should all feel indebted to Dr Fry for his meticulous record-keeping and for his realistic appreciation of the difficulties and responsibilities of those in charge of a hospital's casualty department His excellent paper will provide a basis for intelligent planning, and perhaps a challenge to revise the accepted ideas, if such there be, on junior and consultant staffing of casualty departments

London, W 1 A DOYNE BELL

TREATMENT OF ADVANCED CARCINOMA OF THE BREAST BY OOPHORECTOMY AND PREDNISONE

SIR,—The paper by Dr Brinkley and Dr Pillers (Jan 16) encourages us to place on record our experience with a similar regime at this hospital Our series was started in June, 1956, and totals 46 cases To date we have withheld publication in view of the small number of patients involved, the difficulty in assessing results, and the relatively short follow-up (three years and seven months)

We have found the age, menopausal status, and tumour-cell type to be of no help in predicting the outcome in any given case An attempt to assess the degree of possible adrenal suppression has been made in all cases by serial estimations of urinary ketosteroid and œstrogen excretion levels This has been a laborious procedure So far as we can judge the fall in these levels bears no relation to the clinical results, that is to say, in some cases on whom a satisfactory remission has been obtained the levels of both remained within low normal limits

The presence or absence of metastases in the ovaries also bears no relation to the outcome of the case It has seemed to us desirable in selecting cases for oophorectomy to extend the upper age limit certainly to 65 years, and possibly later in a few others

We have found it easier in most cases to demonstrate arrest of progress of metastases rather than objective evidence of regression In a few patients large ulcerative lesions of the chest wall have completely healed and in others bony consolidation of deposits and regression of pulmonary lesions has definitely occurred Symptomatic relief has, however, been common

In this series we have not noticed any increased tendency to the formation of ascites, pleural effusion, or œdema of the arm as might have been expected with steroid therapy, rather in fact some patients who had required frequent chest aspirations of large pleural effusions for their comfort have ceased to require this procedure completely

There are some disadvantages to this therapeutic programme In the series there was one case of sudden death from massive hæmorrhage from an acute peptic ulcer and in one case not included in the series death occurred following perforation of a peptic ulcer We have endeavoured to exclude patients with past histories of peptic ulceration or accepted them for treatment only after barium-meal examination In all cases it has been our practice to prescribe routine alkali therapy with the prednisone We have also excluded patients with active or only recently quiescent tuberculous lesions It must be recognised that patients with associated diabetes mellitus present considerable therapeutic problems as a result of steroid therapy

It is necessary to warn practitioners against the dangers of sudden withdrawal of the prednisone in patients who may develop an emergency condition

In our 46 cases, 25 are now dead, 10 surviving less than six months, 8 obtained arrest of their disease for periods in excess of twelve months, 4 for two years and 2 for two and a half years It might be noted here that in 4 patients coming to necropsy when particular attention was paid to the adrenal glands, although there appeared to have been some reduction in their overall mass, no histological change had occurred

Among the survivors still under treatment, 1 patient is alive and well after three years and seven months (she had a large fungating local recurrence in the chest wall, complicated by severe secondary hæmorrhages from the surface of the ulcer, which failed to respond to any other form of treatment) 1 patient is alive and well after three years, 1 at two and a half years and 5 after twelve months 6 patients have survived more than six months

We feel that one must assess benefit not only by length of survival but also by the quality of the life lived by the patients in the interval before death Even in some of our disappointing cases there is no doubt in our minds that distressing symptoms have been considerably ameliorated

We feel that this regime is a valuable approach to the problem of the patient with widespread metastatic breast cancer when the only alternatives are adrenalectomy, hypophysectomy, or pituitary destruction These are big undertakings, to the patient and surgeon alike, for on the one hand they are not without hazard and on the other, improvement cannot be promised with certainty in any given case

It may suffice to say that since the evolution of this line of therapy bilateral adrenalectomy or hypophysectomy has been a very infrequent procedure at this hospital

We are grateful to Dr Cameron, of our biochemistry department, for his help with the endocrine estimations

St George's Hospital,
London, S W 1

ARNOLD ELLIS
VICTOR RIDDELL

A CENTRAL LABORATORY FOR OCCASIONAL INVESTIGATIONS

SIR,—I support Dr Hughes-Davis (Jan 2) in his suggestion for reference laboratories for occasional investigations, requests being referred by a pathologist

In addition I should welcome contact with a special laboratory under the control of the National Health Service where one could obtain an occasional check of any of the more unsatisfactory routine estimations—e g, serum uric acid, diastase, high bilirubins A specialist laboratory should attract the necessary calibre of trained biochemists if adequate finances were available

We now regularly use the freeze-dried serum prepared by arrangement with the Association of Clinical Pathologists, &c, but this only, at present, allows the extra check of seven of the more simple estimations

Fletcher Laboratory,
Royal West Sussex Hospital,
Chichester, Sussex

PHYLLIS DAGNALL

INDUCTION OF ANÆSTHESIA IN YOUNG CHILDREN

Sir,—Dr Hodges' thoughtful article (Jan 9) is of interest to all who have the handling of children at heart The difficulty in all this work is to devise an absolute standard of behaviour pattern. Doughty[1] first drew attention to this need, and he has done much work since Using a similar classification to his I did a controlled series of 100 cases, comparing premedication with atropine only, with a methylpentynol/hyoscine mixture given by mouth A summary of my results was

	Premedication	
Reaction	*Atropine only*	*Methylpentynol/ hyoscine*
Smiled	5	12
Impassive	18	26
Winced	16	2
Cried	11	10
Total	50	50

All cases were induced with intravenous thiopentone

I still feel that we should help the "self-controlled but guarded" cases of Dr Hodges, provided this can be done with safety, and for this purpose I still find the methylpentynol/hyoscine mixture valuable

Recent correspondence in the *Medical Journal of Australia*[2–5] again raised the matter of the incidence of vomiting during induction after premedication with methylpentynol in the form of 'Oblivon' elixir

Rendell,[6] in the first article on the clinical use of methylpentynol, did state " in about a tenth of the cases induction was delayed by vomiting " It is unfortunate that this statement has been copied many times, including in the new textbook on anæsthetics by Wylie and Churchill-Davidson, because on closer reference to Rendell's article it is stated that " though normally premedication was given 1 hour before operation, half to 2 hours or more proved satisfactory "

In my original article,[7] in which I quote from over 500 cases, I stated that " no difficulty from vomiting on induction has been observed. I think the difference in my series is due to the fact that the methylpentynol had been given at least 1 hour before induction "

I R McDonald stated[3] that he passed a Ryle's tube on 4 successive cases premedicated with this drug and that the minimum volume aspirated was 8 oz (230 ml)

This obviously needed verification. During routine tonsil lists I therefore passed a small plastic œsophageal tube under direct vision after the patient had been induced and was on the table with the Boyle-Davis gag in position The presence of the tube in the stomach was confirmed by auscultation over the epigastrium The following were my results

	Premedication				
Age (*yr*)	*Elixir oblivon* (*drachms*)	*Hyoscine* (*gr*)	*Time given*	*Time of aspiration*	*Volume*
10	4	1/100	8 45	10 15	1 ml
3	2	1/150	8 45	10 15	nil
7	3	1/100	8·45	10 45	nil
7	3	1/100	9 0	11 10	nil
6	3	1/100	9 15	11 30	nil
12	4	1/100	8 30	10 0	10 ml
6	3	1/150	8 45	10 15	nil
5	2	1/150	9 0	10 40	1 ml

In no case was the stomach aspirated less than $1^1/_2$ hours after the premedication this I am sure is the secret of success with this method The hyoscine is dissolved in the methylpentynol so that no preoperative injection of atropine is necessary I still find this a very safe and satisfactory premedication for children

Worthing F R Gusterson

Sir,—Dr Hodges' article prompts a few reflections from me As an early worker on the effects of hospital on young children I noted that " the operation for the removal of tonsils seems to be very traumatic, out of all proportion to its severity "[1] It was therefore very reassuring to note how, with modern methods, the trauma of the anæsthesia and the surgery could be reduced to a minimum

I was the more interested however in Dr Hodges' other finding—namely, that " factors other than anæsthesia may be more often responsible for psychic trauma ", and he specifically mentions homesickness This would correspond to the psychiatrists' " emotional insecurity " (or overdependence) a feeling which, as explained in my monograph, is the key to the whole problem of hospitalisation One does not so much ask for special methods in hospital, I take it for granted that every effort is made to minimise the unpleasantness of the procedures there But one must always be prepared to find a few children for whom *the hospitalisation itself* is the distressing experience These are the potential cases of neurosis and may need added or special attention The majority of children, with normal sympathetic handling, " digest " and overcome the experience not so these few who fail on account of some inner problem making them the more vulnerable

Leeds H Edelston

CONTROL OF ANTICOAGULANT THERAPY

Sir,—Dr Matthews and Dr Walker (Dec 26), referring to the one-stage prothrombin-time, state " It is familiar to clinical pathologists and hospital doctors in general who, despite its theoretical and practical shortcomings, have confidence in the method and find it tolerably safe " Such a statement impugns not merely the reliability of the original test but also that of other procedures, especially the thromboplastin generation test, since the last step in the latter method is essentially a one-stage prothrombin-time

What are the theoretical shortcomings ?

The one most commonly cited is that a prolonged prothrombin-time is generally not due to a decrease of prothrombin When the test was developed, such factors as thromboplastin and prothrombin were recognised primarily as activities, and it was found by both the one- and two-stage methods that the level of prothrombin in the blood markedly dropped in vitamin-K deficiency and after the administration of dicoumarin With the observation[2] that the delayed prothrombin-time of stored oxalated human plasma could be completely corrected by the addition of fresh plasma depleted of prothrombin by adsorption with $Al(OH)_3$ or plasma from an animal given dicoumarin, it became evident that the test was also sensitive to a new clotting factor hitherto unrecognised It is now established that the test is not only sensitive to this factor (labile or v) but also to stable factor (vii) and to the less well-defined Stuart-Prower factor By adding to the patient's plasma a minute amount of labile factor in the form of deprothrombinised rabbit plasma, the prolonged prothrombin-time in congenital labile-factor deficiency is corrected to the normal of 12 seconds Likewise, the prothrombin-time is corrected to 12 seconds by the addition of normal aged serum in stable and in Stuart-Prower deficiency

Only in true hypoprothrombinæmia is there no correction effected by either adsorbed rabbit plasma or aged serum. Thus, by simple modifications of the one-stage method, it can be made specific for any of the known factors in the prothrombin complex. What is called a shortcoming is actually a pillar of strength The newly alleged shortcoming—namely, that it is not sensitive to the contact factor—would, no doubt, be serious if we had glass-lined blood-vessels

Interestingly, Matthew and Walker found a good correlation between the thrombotest and the Quick test while the " correlation between thrombotest and the P & P test was not quite so good" Yet, only a relatively short time ago, the latter test was introduced as a much superior test to the basic one-stage method The logic of how all this is likely to "confirm it (thrombotest) as the best laboratory procedure for the control of anticoagulation therapy" is somewhat elusive

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[1] *Brit J Anæsth* 1957, 29, 407
[2] McDonald I H *Med J Aust* 1959, ii, 417
[3] McDonald, I R *ibid* p 541
[4] McDonald, I H *ibid* p 740
[5] Gusterson F R *ibid* p 829
[6] Rendell C M *Brit med J* 1954, ii 1397
[7] Gusterson, F R *Lancet*, 1955, i, 940

[1] Edelston H Separation Anxiety in Young Children Genetic Psychology Monographs 1942
[2] Quick, A J *Amer J Physiol* 1943, 140, 212

Department of Biochemistry,
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ARMAND J QUICK

CHROMOSOME STUDIES IN LEUKÆMIA

SIR,—The calculations for 8 cases of chronic leukæmia (3 myeloid and 3 lymphatic) referred to in our letter of Jan 16 are shown in the accompanying table

DISTRIBUTION OF CHROMOSOMES COUNTS IN CHRONIC LEUKÆMIA

	Patient	<41	41	45	46	47	48	>48	Totals
Chronic myeloid leukæmia	H51	0	1	6	36	2	2	0	47
	H61	0	1	0	22	0	1	0	21
	H73	0	2	4	16	0	0	0	22
	H229	0	3	0	15	0	0	0	18
	H237	1	2	3	26	0	0	0	32
	Total	1	9	13	115	2	3	0	113
Chronic lymphatic leukæmia	H82	2	0	0	19	0	0	0	21
	H238	0	0	4	27	1	0	0	32
	H250	2	1	1	16	1	0	0	21
	Total	4	1	5	62	2	0	0	71

		Modal	*Non modal*	χ^2	P (n = 1)
C M L	Expected	121 6	21 4	2 40	>0 1
	Observed	115	28		
C L L	Expected	62 9	11 1	0 09	>0 7
	Observed	62	12		

Medical Research Council Group
for Research on the General Effects
of Radiation,
Western General Hospital,
Edinburgh
A G BAIKIE
W M COURT BROWN
PATRICIA A JACOBS

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—We are discussing a very little understood condition, which in some ways might be classed with congenital deformities, and in others with new growths May I suggest a name for it which I have used for many years—"the spreading angioma of infancy"? Nævus is a meaningless term, including stains and moles, "strawberry" as an adjective applies only to minor degrees, and there is nothing in them resembling caverns But they do belong to the vast and varied group of angiomata, they do grow, and this growth does occur in infancy

I wrote about one stage in the natural history of one type of these angiomata, the small but growing spot on the face which appears at or soon after birth They are often described by the mothers, who alone at this stage worry about them, as having started like a gnat-bite or a little scratch They are seen by general practitioners, doctors in clinics, pædiatricians, and obstetricians, but I have never known them at this stage to be referred to dermatologists or plastic surgeons This correspondence has made it clear what would happen if they were What they are apt to grow into is shown by the accompanying photographs, and the question I raised was whether this horrible development could be stopped

It must be clearly understood that it is not treatment at the stage illustrated which I am discussing, but treatment to avoid its occurrence

On the comparatively rare occasions on which I find these growing red spots I have been treating them by subcutaneous injections of saturated salt (sodium chloride) solution, which is non-toxic but extremely caustic, if injected into the skin it will cause a slough I get the impression that the violent cellular reaction produced in the deep tissues by this will begin the process of regression, at any rate none treated in this way has run wild as they so often do if left alone Supposing one were to get a hundred of these "surgical emergencies"—the growing red spots on the face—treat them with these injections, and find that there were no disfigurements of the kind shown one would have some interesting though inconclusive information It would be inconclusive because it would be impossible to prove what would have happened had nothing been done, but then so much medical information is of this type

I have also been pleased with the results of injecting comparatively large quantities, up to 5 ml, into that type of angioma which closely mimics a rapidly growing sarcoma of the face, a deep elastic swelling with a faint blue tinge, under skin which at first is intact This type again is not referred to dermatologists or plastic surgeons, it sets difficult problems of diagnosis and treatment to the general surgeon

As to other methods of treatment, I dislike X rays, though they are undoubtedly effective during the period of rapid growth Carbon-dioxide snow is obviously completely futile on any but the very superficial types which are best left alone A primary excision is often the best as well as the most obvious treatment, it saves the mother years of embarrassment, and in

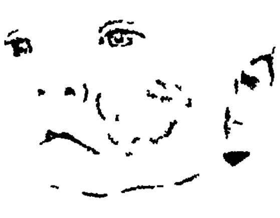


Fig 1

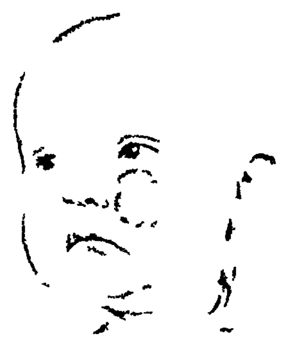


Fig 2

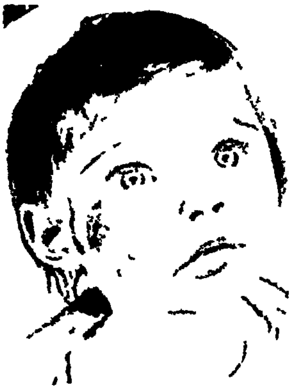


Fig 3

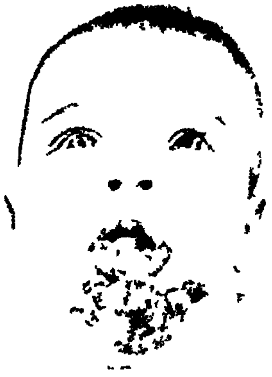


Fig 4

Fig 1—Angioma at stage of full growth, and beginning regression Started as small spot will end as mass of redundant fibrous tissue

Fig 3—Similar case to figs 1 and 2 showing a more advanced stage of regression with a baggy scar of the cheek

Fig 2—Similar case to fig 1

Fig 4—An angioma at the stage of rapid growth showing many points at the "gnat bite" stage It is obvious that bad scarring will result, and excision of the redundant tissues of the lip be necessary

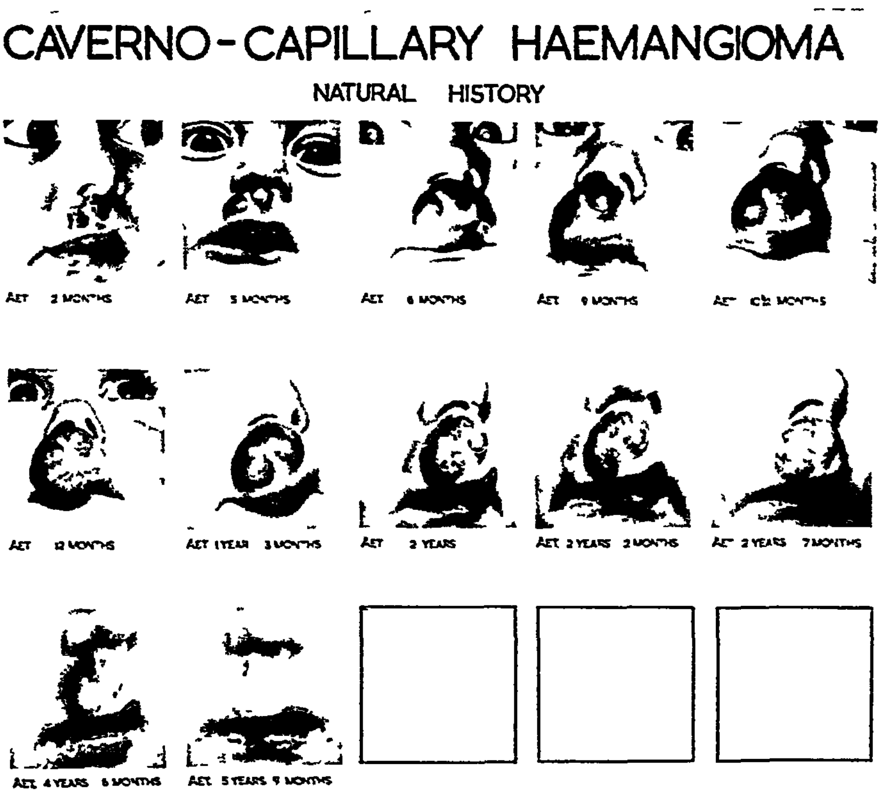
y case often has to be done on e sagging mass of fibrous tissue ft when regression is complete The substances used for scler- ing veins are unsuitable, being o toxic in the tissues The athermy needle, insulated ex- pt for its point, is useful, but I ave been afraid of injuring a erve with it.

But I realise that a concerted vestigation of the kind I ave suggested is impossible the present fragmented tate of my profession

ondon, W 1 DENIS BROWNE

SIR,—I have been very in- erested in the extensive cor- espondence on this subject, hich was also debated at ome length at a meeting of he Dermatological Section of he Royal Society of Medicine eld at The London Hospital n June 18, 1959

My experiences conform losely to those of Dr Simp- on (Dec 12) and I also follow Mr Murley's plan (Jan. 9) of howing photographs to the parents



Some of your readers may be interested to see a series I collected in the past six years—not yet complete but very valuable for indicating to an anxious mother that Nature is on the side of recovery The large hæmangioma has disappeared at 5 years 9 months, leaving a residual soft fleshy excess of tissue which it is anticipated will disappear within the next few years The three blank spaces are for later photographs

Acknowledgment is due to the photographic department of The London Hospital

London, W 1 BRIAN RUSSELL

SIR,—In view of Dr Simpson's series and other meticulously followed-up and carefully analysed series illustrating the natural history of cavernous hæmangiomata, it astonishes me to find that anyone can strongly disagree, as Dr Millington (Jan 16) does, with these findings, which have been amply confirmed by the vast majority of dermatologists and plastic surgeons, when his sole criterion of satisfaction regarding his series of 1000 irradiated children is that "in a confined community such as this one would expect to be made aware of any untoward sequelæ of treatment"

Quite apart from unhappy sequelæ of irradiation, which Mr McLaughlin (Jan 16) so rightly deplores, Dr Millington's statement about "doubtful hopes of natural resolution" is in no way supported by the facts

Princess Margaret Hospital,
Swindon K D CROW

SIR,—Dr Simpson's article on strawberry nævi and the subsequent correspondence have interested me greatly I have studied 152 consecutive children with 191 strawberry nævi, first seen between 1950 and 1953 Particular care was taken to make the follow-up as complete as possible, and the 9 children who were untraced are all known to have moved away from the district It is unlikely that they would have done this simply to seek surgical aid The results, which are being prepared for publication, are in complete agreement with Dr Simpson's and lend strong support to the view that conservative treatment is the best policy

Gloucestershire Royal Hospital,
Gloucester R E BOWERS

HYDROFLUMETHIAZIDE

SIR,—With great interest I read the article[1] by Dr Edmonds and Professor Wilson A brief remark on p 308 deserves attention because it may contribute to removing the confusion which seems to prevail regarding the conception of the kaliuretic effect of the various derivatives of chlorothiazide and its theoretical background It reads "Hydroflumethiazide also possesses the sulphonamide group, and probably its lack of effect on bicarbonate excretion results from the much smaller quantity used"

Hydroflumethiazide and hydrochlorothiazide have a chloruretic effect which is about 15 times greater than that of chlorothiazide, as a consequence when using them the quantity of sulphonamide supplied is about 15 times smaller than when using chlorothiazide, to obtain a certain chloruretic effect. Consequently the excretion of bicarbonate and therefore the kaliuresis are smaller However, it is doubtful whether these differences in "the primary kaliuretic effect" are of any therapeutic importance Experience shows that a potassium supplement is often necessary in prolonged treatment with all existing preparations of this group of diuretics, and it is very probable that the potassium loss is more closely connected with their chloruretic effect, as is the natriuresis, whereas the kaliuresis which is connected with the inhibitory effect on carbonic anhydrase is relatively small in comparison (although it is of course the smaller the less sulphonamide they contain in proportion to their chloruretic effect)

Of far greater therapeutic importance is undoubtedly "the secondary kaliuresis", which in certain patients may arise after administration of all potent diuretics with natriuretic effect, and which is a consequence of the increased secretion of aldosterone initiated by the organism as a "defence" against the increased natriuresis (as well as against too rigorous restrictions of salt in the diet) Recognition of this condition, and its treatment, are only in the embryo stage, but the introduction of spirolactone opens a wide field

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[1] *Lancet*, 1959, ii, 303

A great deal of unnecessary discussion as to whether one diuretic should be preferred to another, especially with reference to the kaliuretic effect, might, however, be avoided if we (1) keep this quantitative situation of the sulphonamide group in mind, and (2) in each individual case try to establish whether the kaliuresis is primary or secondary

Hillerød, Denmark TORBEN ANDERSEN

FRUCTOSE TREATMENT OF PHENYLKETONURIA

SIR,—Some of our patients suffering from phenylketonuric oligophrenia have not been able to keep to their low-phenylalanine diets for various reasons Geisler and Stroder[1] reported that they were able to increase the phenylalanine tolerance and decrease the phenylketonuria of such patients by giving fructose intravenously or orally In order to see if fructose feeding (6 g per kg) would help our patients we tested two known phenylketonurics who have been receiving a normal diet at home

CASE 1 —A boy (H S C 208562) aged 8 years was first seen at the age of 2½ years suffering from frequent fits, deafness, and mental backwardness His general I Q was 20 and his plasma contained 30 mg per 100 ml phenylalanine and his urine contained phenylpyruvic acid Although treatment with a low-phenylalanine diet was started and his general I Q rose to 30, he failed to keep to the diet and has received a normal diet for the past four years (general I Q now 13)

CASE 2 —A girl (H S C 265841) aged 5 years was first seen at the age of 2 years because of frequent fits and mental retardation Her general I Q was 20, plasma-phenylalanine 30 mg per 100 ml, and her urine contained phenylpyruvic acid After eighteen months' treatment with a low-phenylalanine diet the general I Q rose to 30 and then remained stationary when the diet was not being adhered to For the past eight months a normal diet has been taken and the general I Q has fallen to 20 again

Each patient was fed on (1) a normal diet, (2) the same normal diet except that fructose 6 g per kg daily was substituted for all the sucrose or glucose normally taken, and (3) a normal diet again The fructose supplied all the sugar that was needed in the diet Plasma levels of phenylalanine were estimated by the comparison of paper chromatograms of known standards and desalted plasma Urine phenylpyruvic acid levels were estimated by the method of The, Fleury, and Vink[2] The results are shown in the accompanying table

EFFECT OF FRUCTOSE DIET ON PLASMA-PHENYLALANINE AND URINE PHENYLPYRUVIC-ACID LEVELS

Case	Diet	Plasma phenylalanine (mg per 100 ml)		Urine phenylpyruvic acid
1	Normal diet for the past 4 years, tested for 4 days	30		100–400 mg per 100 ml
	Fructose substitution (120 g per day) for 14 days	30		100–400 mg per 100 ml
2	Normal diet for past 8 months tested for 4 days	30		70–200 mg per 24 hr
	Fructose substitution (120 g per day) for 8 days	50		50–220 mg per 24 hr
	Normal diet for 21 days	-		50–500 mg per 24 hr
	Fructose diet for 19 days	First day	50	Ferric-chloride test strongly positive daily
		Last day	50	

Bearing in mind the fluctuations in daily urine phenylpyruvic-acid excretion, it is seen that fructose feeding was not associated with any marked changes Plasma phenylalanine levels also were not affected favourably Close observation in the ward showed that no changes in behaviour in either patient were associated with fructose feeding (Mr Stephen Coates)

Fructose feeding does not appear to have been of use in the treatment of these two patients suffering from phenylpyruvic oligophrenia

We should like to thank Mrs M B Hummerston, of the dietetic department, Sister E M Baldwin, of the metabolic ward and Mr Stephen Coates, senior clinical psychologist, for their invaluable help in this investigation

Institute of Child Health and
The Hospital for Sick Children,
London W C 1

A A MONCRIEFF
R H WILKINSON

REMOVING A SAFETY-PIN FROM THE BRONCHIAL TREE

SIR,—Would I be wrong in suggesting that Chevalier Jackson demonstrated Mr Donald Barlow's device (Jan 23) for removing an open safety-pin from the bronchial tree some 30 years ago?

The story was told in America that when Chevalier Jackson was tossing open safety-pins into an anæsthetised dog's trachea, a mild little man at the back of the room asked if he could have a go He mastered the technique, caught the night train, and removed the open safety pin from the trachea of his infant patient

London, W 1 W HARGRAVE-WILSON

KEROSENE (PARAFFIN) POISONING

SIR,—Ingestion of kerosene (paraffin oil) is a common cause of accidental poisoning, particularly in children. Recent animal studies by the Medical Research Division of Esso Research and Engineering Company, Linden, New Jersey,[3] have shown that kerosene poisoning is principally due to aspiration of the material into the lungs, where the kerosene produces a chemical pneumonitis The volume of kerosene required to produce a pneumonitis is very low thus, kerosene by aspiration into the lungs is highly dangerous By contrast, large amounts of kerosene can be ingested without pulmonary injury or ill effect

The accompanying table shows the oral toxicity of common liquid chemicals

ORAL TOXICITY OF COMMON LIQUID CHEMICALS

Chemical	LD_{50} (mg per kg)	Toxicity class
Acetic acid (rat)	3310	Slightly toxic
Lactic acid (rat)	3730	Slightly toxic
Isopropyl alcohol (rubbing alcohol) (rat)	5840	Practically non-toxic
Acetone (rat)	9750	Practically non-toxic
Ethyl alcohol (rat)	13 660	Practically non-toxic
Glycerine (rabbit)	27 000	Relatively harmless
Kerosene (rabbit)	28 350	Relatively harmless

If oral toxicity is low (high LD_{50}) the probability of systemic intoxication is low and removal of kerosene from the stomach is unnecessary

Clinical kerosene poisoning is probably due to aspiration of a relatively small volume of kerosene during or shortly after swallowing rather than to blood borne kerosene absorbed from the gastrointestinal tract. Since the oral toxicity of kerosene is low, the treatment should not include the induction of vomiting or other clinical procedures such as passage of a stomach tube for gastric lavage which may induce vomiting and thus aspiration. (The present teaching in the first-aid manuals of the various societies is "Make the casualty vomit. Give copious draughts of water") Since anti-emetics are central-nervous-system depressants, they are contraindicated because sedation and stupor are frequently found in kerosene poisoning Positive measures recommended are (1) oxygen if necessary, (2) antibiotics prophylactically, for the prevention of secondary bacterial pneumonia, (3) if the patient is conscious, ingestion of a vegetable oil or ice-cream to dilute the kerosene, diminish the rate of absorption into the blood, and soothe the inflamed mucous membranes of the gastrointestinal tract.

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[1] Geisler, Von E , Stroder, J *Ann pædiat* 1958 191, 147

[2] *The, F P, Fleury, P, Vink, C L J Clin chim acta* 1957, 2, 471

[3] *Gerarde, H W Delaware St med J* 1959, 31 276

Esso Petroleum Co ,
London, S W 1

ERNEST H CAPEL
Chief Medical Officer

Esso Petroleum Co
Fawley

A WARD GARDNER
Senior Medical Officer

THE PREP SCHOOL

SIR,—I was most interested to read the admirable review of the I A P S report *Foundations* in your issue of Jan 2 In it you refer to the difficulty of finding suitable masters, and I thought you might be interested to know the steps that our Association takes to train those who teach in its schools

A joint committee of I.A P S and the Oxford Institute of Education runs an eighteen-month training course on a correspondence basis with four short residential periods This is for young men and women who have recently taken up teaching In 1958 and in 1959 we put on a week's residential course at Oxford for men leaving the Services and intending to teach in our schools These courses had the approval of the Resettlement Board and were so successful that we hope to run another this year

Residential refresher courses are held for a week every April in Oxford for headmasters and their staffs, to ensure that the latest developments and methods in education are brought to their notice

Swanbourne House School,
Swanbourne, near Bletchley,
Bucks

H A C EVANS
Chairman Incorporated Association
of Preparatory Schools

LEISHMANIASIS ACQUIRED BY CONTAGION

SIR,—Professor Symmers is to be congratulated on his paper of Jan 16 which has made history, and is moreover most intriguingly and fascinatingly written. It certainly gives rise to new appraisals and causes students of this subject most furiously to think.

The outstanding facts are that it is possible for a man suffering from *Leishmania donovani* infection to pass it on by sexual intercourse to his wife, thus producing a local lesion in the vagina, to all extent and purposes resembling an oriental sore (attributable to *Leishmania tropica*) At first sight this course of events suggests that current beliefs need revising However, there may well be another explanation in the true ætiology in the analogy of Kenya kala-azar, where cultures of *L donovani* isolated from the gerbille, *Tatera vicina*, in the leptomonas stage, when inoculated subcutaneously into volunteers, gave rise to a local lesion, known as a leishmanioma [1] This is probably analogous to the primary lesion of epidemic kala-azar and which was first described by Clinton Manson-Bahr [2] in North Kenya It is from this leishmanioma on the tibiæ that the organisms spread throughout the body to subsequently produce the classical picture of visceral leishmaniasis (or kala-azar)

But more disturbing than this, from the viewpoint of the student of tropical medicine, is the recital of what may be called "a tragedy of errors" It is a sad commentary on the efficacy of the ancillary services of present-day medicine. From the viewpoint of the consultant in tropical diseases I would venture to suggest that these avoidable mistakes arise primarily from the neglect of the fundamental principles of clinical medicine—the taking of a case-history How often one observes that the obvious diagnosis has been missed by neglect to do so, to find out, for instance, whether the patient has recently come from the tropics, subtropics, or other foci of endemic disease It is perfectly correct to state that the incidence of tropical infections has been much reduced, but it does not mean that they have been entirely swept away

London, W 1

PHILIP MANSON-BAHR

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[1] Manson-Bahr, P E C *Trans Roy Soc trop Med & Hyg* 1959, 53, 123–126

[2]. Manson Bahr, P E C *ibid* 1956, 50, 465–471

PREVENTION AND TREATMENT OF BEDSORES BY SILICONE CREAM

SIR,—Much work has been done with silicone creams and emulsions in the prevention of bedsores Controlled trials showed that emulsion or cream must contain 20% silicone to be effective.[1] Products with less than 20% silicone were ineffective, and additional silicone over 20% did not increase the efficiency of the cream or emulsion

Silicone emulsions in the prevention and treatment of bedsores have now been used by the district nurses in Flintshire since 1954 with very good results They have the following advantages (*a*) they are more effective than soap, water and spirit, and (*b*) they show a considerable saving of nursing time in the treatment of pressure-points Recently two new silicone preparations have been given a trial in this county and have proved more effective than plain silicone emulsion

One cream (bedsore cream I) contained 20% silicone fluid MS200, 0 05% phenylmercuric dinaphthylmethane disulphonate ('Penotrane'), and 0 5% dienœstrol. The other (bedsore cream II) contained the same amounts of silicone and penotrane but omitted the dienœstrol Both creams were of pH 4 2, approximating to that of normal skin.[2]

District nurses who had considerable experience of silicone emulsions tried each of these creams in a number of patients The record cards kept by the nurses show that both creams were more effective than plain silicone emulsions in the prevention and treatment of bedsores Ten patients were treated with cream II (penotrane/silicone cream) and eight with cream I Cream I seems more effective but it is only fair to emphasise that the number of cases treated so far is small

The advantages of the new cream can be summarised as follows

(1) They produce more rapid healing of damaged skin over pressure-points than do plain silicone emulsions
(2) They appear to be more effective in penetrating the skin, and more efficient in protecting the skin of incontinent patients
(3) They are easy to apply and repeated applications do not tend to "cake" on the skin

As many hospitals and local health authorities are now using silicone emulsions, these small trials with the new silicone creams might be of interest.

The two creams used in the trial were kindly supplied by Messrs Ward, Blenkinsop, from whom the plain penotrane silicone cream is now commercially available The cream containing penotrane and dienœstrol is only available for clinical trials at present

County Health Offices,
Mold, Flintshire

G W ROBERTS

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[1] Roberts G W *Lancet* 1959, i, 1207

[2] Harry, R G *Brit J Derm* 1942, 54, 1

DENTAL CARIES

SIR,—I was very pleased to see in your leading article of Jan. 16 that the importance of Stack's protein is recognised, as well as its significance in relation to the observations that caries is primarily a deficiency disease (The term "Stack's protein" is preferable to "soluble protein" as it is only soluble under pathological conditions) Indeed, there is now sufficient evidence available for one to be still more precise about the mechanism of the carious process

You state that "about equal quantities of each type of protein are present in the interprismatic spaces, and the soluble protein is assumed to be the first part of the tooth substance to disappear" It is not quite clear what is meant by "interprismatic spaces" The electron-microscope photograph (fig 1) shows the distribution of the two proteins in dental enamel before calcification The denser keratin is in the prism walls and Stack's protein in both prism core and interprismatic regions[1] When calcification occurs, apatite crystallites are deposited in, and protected by, both proteins[2] Professor Darling and his coworkers have shown that the first stage of the carious process is the degradation and/or solution of Stack's protein[3 4] This presumably exposes its apatite crystallites to further attack, and fig 2 shows the state of affairs in chalky enamel, which is the second stage of the carious process Here the prism walls remain normal, but without Stack's protein the crystallites which had been protected by it have mostly gone

It seems probable that the stability of the protein is determined at the time of its polymerisation,[5] and that vitamins or trace elements act as catalysts in the process There is abundant evidence from all parts of the world to show that the incidence of caries is related to diet Lady Mellanby[6] showed that vitamin D, which reduces the incidence of caries, affects the matrix, and the paper quoted on vitamin B_6[7] shows that other vitamins have to be considered too Clinically it is known that fluorine causes a very substantial decrease in caries incidence, and experimentally Darling and Brooks[8] have shown that fluorine also modifies matrix production At present there is not sufficient evidence to show whether caries is primarily a vitamin deficiency, a fluorine deficiency, or a combination of the two, but there is nothing against the belief that fluorine is the more important

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1 Little, K *J R micr Soc* 1959, 78, 58
2 Little, K *J dent Res* 1957, 36 815
3 Darling, A I *Brit dent J* 1958, 105, 119
4 Darling A I, Mortimer, K V *J dent Res* 1959, 38, 1226
5 Little, K Proceedings of 4th International Conference on Electron Microscopy, 1958
6 Mellanby, M *Spec Rep Ser med Res Coun, Lond* 1934, no 191
7 Strean, L. P et al *N Y St dent J* 1958, 24 133
8 Darling, A I, Brooks, A W *J dent Res* 1959, 38, 1226

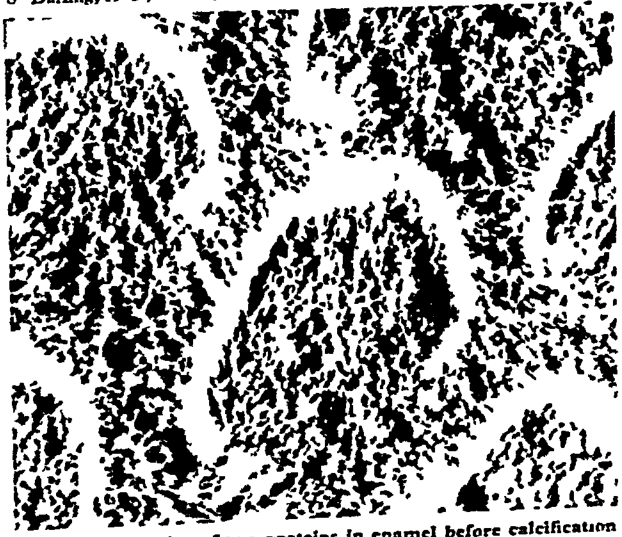

Fig 1—Distribution of two proteins in enamel before calcification (× 7500)

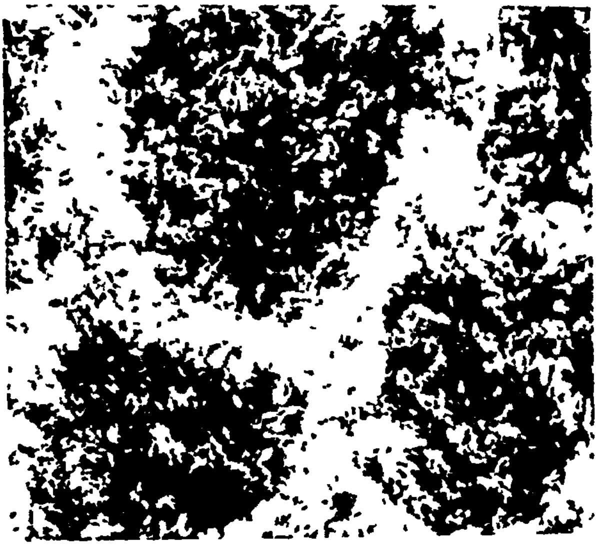

Fig 2—Chalky enamel, the second stage of the carious process (white object on black background) (× 7500)

The other main factor which is a practical consideration in the prevention of caries is the prevention of solvents from reaching the vulnerable protein In perfectly formed teeth this is achieved by means of the surface zone But it is of interest to remember that there are many instances of the surface zone being worn away in "uncivilised" communities without caries resulting Acids and oxidising agents are undoubtedly partly responsible for caries, but when one examines critically the evidence for bacteria and refined sugar, traditionally regarded as causative factors, their claim seems to be curiously elusive The bacteria appear in large numbers only after the carious process has been initiated They are very probably more resistant to degradation than Stack's protein, so that it is worth considering whether components of toothpastes aimed at bacterial degradation are not even more likely to affect the Stack's protein, if this is exposed by abrasion or attrition

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K LITTLE

TREATMENT OF CUSHING'S SYNDROME

SIR,—Dr Montgomery and his associates[1] have commented on this very important problem by describing the occurrence of large pituitary tumours (one malignant) after adrenalectomy in 2 cases of their own and by collecting similar cases from the literature They conclude that " possibly in the future we shall have to consider hypophysectomy as an alternative to adrenalectomy more often than we do at present"

On the basis of 36 years' experience with the many aspects of Cushing's syndrome (my first case observed in 1923 was included by Cushing in his original description of the disease entity named after him[2]), I should like to offer yet another alternative—hands (that is, surgical hands) off the majority of patients who fall under this, of late, very loose heading Of course I do not wish to imply that patients who are suspected of harbouring a carcinoma or even an adenoma of the adrenal cortex should be kept from surgery I am referring to the vast majority of patients who have no evidence (e g, in air-insufflation studies) of a gross adrenocortical lesion, unilateral or bilateral, or the full-blown clinical symptomatology, or at least gross hypertension which by itself may justify operation. In such patients the presenting symptom is commonly the characteristically distributed obesity with moon face and purple striæ associated with mild to moderate hypertension and or diabetic tendencies (often very unstable) and with little or no abnormality of steroid excretion. In these formes frustes an attempt may in my opinion be made with a rigid dietary reg-

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1 Lancet, 1959, ii 70
2 Cushing, H *Bull Johns Hopk Hosp* 1932, 50 137

men, supported by appetite depressors and possibly by the judicious use of dehydration. As I have often emphasised,[3–7] very satisfactory results can thus be obtained, comparable to the remissions after surgery Of course, relapses do occur, but so they do after surgery, moreover, this conservative therapy can be repeated at will, without fear of untoward side-reactions If the patient fails to respond, an attempt may and indeed should be made with X-irradiation to the pituitary region before surgery is considered

I agree that this treatment is neither infallible nor ideal Nevertheless, I was led once more to stress the conservative method in the treatment of Cushing's syndrome after reading Dr Montgomery's paper, which illustrates not only the well-known risks of adrenalectomy—namely the Scylla of adrenal insufficiency and the Charybdis of a recurrence—but adds to this list the possible development of pituitary tumours which may necessitate yet another and certainly not harmless operation

Jerusalem HERMANN ZONDEK

ELECTRIC SHAVERS AND EYE AFFECTIONS

SIR,—It is now widely conceded that various inflammatory conditions of the eye, and in particular, the conjunctiva, may well be initiated by microscopic fragments of dandruff which lodge in the eye during combing or brushing of the hair I would draw attention to another and more potentially dangerous source of similar irritation and/or self-infection—the electric shaver At least one well-known manufacturer advises users to remove the shaving " head " after shaving and " blow across it " to remove the dust, which is composed, in persons with facial seborrhœa or abnormally dry skin, of powdered skin (or " scurf ") and very small fragments of hair

Many persons almost certainly blow right *into* the shaving head in order to more effectually dislodge the dust, thereby driving some of the dust into eyes, nose, and mouth

When the possible cumulative effect is considered (this is done at least 365 times a year!) the effect on the lungs might also be considered

Cheltenham R ST C ISON

OVERDOSAGE OF PHENELZINE SULPHATE

SIR,—The manufacturers of 'Nardil' (phenelzine sulphate) state that this recently introduced drug provides " safe and effective treatment for the outpatient management of milder depressive illnesses " The following emergency seems worth reporting

A married man, aged 32, was admitted to hospital on Nov 28, 1959, after taking an overdose of 16 tablets (400 mg) of phenelzine sulphate The psychiatric history indicated that during the preceding 12 months he had been increasingly anxious over the payment of hire-purchase commitments Early in October, 1959, he was angry and disappointed on receiving what he considered was insufficient payment for overtime work. He became more anxious, and finally depressed over arrears in his hire-purchase payments He then had a hysterical fugue and wandered to a village some 20 miles away On returning home he was subsequently referred to two psychiatric departments in the area but opted out of treatment at each establishment. On Nov 25, 1959, he became severely depressed and was preoccupied with the idea that he had let his wife and child down badly He was given a supply of phenelzine sulphate tablets by his general practitioner and on the night of Nov 26 took 16 tablets at once Almost immediately he became gay and elated (" I felt champion ") but after some hours became acutely anxious about the possible consequences of his act. His wife took him to hospital where his stomach was washed out Following this procedure he slept deeply for 24 hours By Nov 30 he was reasonably well

This case suggests that the outpatient use of thymoleptic drugs may in fact not be without danger It also seems to confirm that phenelzine is indeed a thymoleptic

It would be interesting to know whether any of your readers have encountered similar cases and what, in general, is the contemporary trend of opinion concerning the outpatient control of medication with thymoleptic drugs

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A BALFOUR SCLARE
J M ATKINSON

ANTIBODIES AGAINST ADENOVIRUSES

SIR,—Data about the incidence and type distribution of adenoviruses in Hungary [1,2] are slight A serological survey, using the methods of complement fixation (C F) [3] and virus neutralisation, was therefore made on various human sera

As an antigen a mixture of the first 7 types of adenoviruses obtained in tissue cultures was used. Neutralisation tests were made in Detroit-6 cell cultures, using adenoviruses of types 1 to 7 separately A total of 1174 human sera were examined by C F and 148 by neutralisation test Results of C F are shown in table I The groups of serum samples were as follows

TABLE I—RESULTS OF C F REACTION

Group	No of sera tested	% of C.F positive	Average titre
1	85	41 (*48 2%*)	1 8 8
2	61	15 (*24 5%*)	1 11 6
3	163	24 (*14 7%*)	1 4 8
4	117	16 (*13 6%*)	1 10 7
5	632	268 (*42·4%*)	1 5 6
6	116	56 (*48 2%*)	1 7 3
Total	1174	420 (*35 7%*)	1 6 5

Group 1—Sera of children, mostly under 5 years, convalescent after an attack of poliomyelitis

Group 2—Sera of persons of 10 to 20 years, in hospital with pulmonary tuberculosis

Group 3—Students of 18 to 20 years of age called for medical examination before admission to the University Medical School

Group 4—Random serum samples from apparently healthy persons over 20 years of age

Group 5—Sera from patients under medical cure with a diagnosis other than disease of the upper respiratory tract

Group 6—Patients with acute respiratory disease

C.F titre values varied between 1 4 and 1 64 for the different groups, and the maximum incidence was within the range 1 4 to 1 8 This observation agrees with the results of others [4] The proportion of positive sera decreased remarkably in those over 40–50

For neutralisation tests some of the sera with positive C.F reactions were selected from all 6 groups The highest incidence

TABLE II—DISTRIBUTION OF NEUTRALISING ANTIBODIES IN 148 SERA AGAINST TYPE 1 TO 7 ADENOVIRUSES

Antibody against	Sera containing antibody
Type 1	93 (*62 8%*)
Type 2	81 (*54 7%*)
Type 3	52 (*35 1%*)
Type 4	59 (*39 8%*)
Type 5	65 (*43 9%*)
Type 6	65 (*43·9%*)
Type 7	73 (*49 3%*)

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[3] Zondek H , Leszynsky, H E. *Brit med J* 1956 i 197
[4] Zondek, H Leszynsky, H E., Zondek, G W *Ann Endocr , Paris* 1957 18 959
[5] Zondek G W , Leszynsky, H E , Zondek, H *Acta med orient* 1957 16 87
[6] Zondek, H Die Krankheiten der Endokrinen Druesen p 569 Basle, 1953
[7] Zondek, H Le Malattie delle Ghiandole Endocrine, p 743 Rome, 1957

[1] Nasz, I , Tóth M , Lengyel, A *Acta microbiol hung* 1958, 5, 267
[2] Béládi, I , Kahan A *Orv Hetil* 1958 99, 224–226
[3] Takátsy, G *Acta microbiol hung* 1955, 3, 191
[4] Zaimann, E , Balducci, D , Tyrrell, D A J *Lancet*, 1955, ii, 595

almost 300% Our figure was based on the price of P A S powders obtaining in July, 1959 Dr Springett is right in suggesting that the drug is cheaper in tablet form, and where both drugs are prescribed its combination with isoniazid effects a further economy

Royal Victoria Infirmary,
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INCIDENCE OF ISCHÆMIC HEART-DISEASE AMONG INDIANS IN KENYA

SIR,—So much has been written about the relationship between fat intake and coronary disease that a statistical survey of the disease amongst the various Indian sections in Kenya might prove of value, since these groups vary so greatly in their animal fat consumption

The Asians, excluding the Goans, may be divided into five main groups

(1) Gujerati, vegetarians (non-Muslims)
(2) Gujerati, non-vegetarians (mainly Muslims)
(3) Punjabi, vegetarians (non-Muslims)
(4) Punjabi, Sikhs (non-Muslims) (Females usually vegetarian and males non-vegetarian)
(5) Punjabi, non-vegetarian (Muslims)

The fat consumption rises in this order from (1) to (5), being least in the Gujerati vegetarians and greatest in the Punjabi non-vegetarian Muslims

TABLE I—NUMBER OF MALE CASES IN EACH GROUP AT DIFFERENT AGES

—	30-39	40-49	50-59	Over 60	Total
Gujerati vegetarians	10	30	44	28	112
Gujerati non-vegetarians	2	17	16	10	45
Total Gujeratis	12	47	60	38	157
Punjabi vegetarians	4	11	18	8	41
Punjabi non-vegetarian Sikhs	1	9	12	10	32
Punjabi non-vegetarian Muslims	2	8	10	6	26
Total Punjabi non-vegetarians	3	17	22	16	58
Total Punjabis	7	28	40	24	99
Total Indians	19	75	100	62	256
Goans	1	14	14	14	43

The population figures have been calculated from the census for 1948,[1] according to which males over the age of 15 number 29,000 Indians and 3000 Goans The Asian population, it is estimated, increased by $2^1/_2$% per annum since that year, but the proportion between the various groups has remained about the same [2] Muslims form 31% and non-Muslims 69% of the Indian population, Muslims thus comprising 9000 and non-Muslims 20,000 males over the age of 15 Hindu males at the same age number 15,000 and Sikhs 3000 Further assessments have been obtained by inquiry from electoral candidates who subdivide their electorates in order to estimate their supporters who come mainly from their own communities, in this way it has been calculated that Gujerati Hindus (vegetarians) outnumber Punjabi vegetarians by about 2 to 1, and that Gujerati Muslims (non-vegetarians) exceed Punjabi Muslims by the same proportion The relative figures of these groups for males over the age of 15 are Gujerati vegetarians 10,000, Punjabi vegetarians 5000, Gujerati Muslims 6000, and Punjabi Muslims 3000

TABLE II—STANDARD DAILY DIETS OF EACH GROUP

Item	Gujerati veg	Gujerati non-veg	Punjabi veg	Punjabi non-veg
Atta	10 oz	9 oz	14 oz	12 oz
Rice	3 oz	3 oz	1 oz	2 oz
Dhall	2 oz	2 oz	3 oz	2 oz
Vegetables	8 oz.	6 oz	8 oz	6 oz
Sugar	3 oz	3 oz	3 oz	3 oz
Meat	Nil	4 oz	Nil	5 oz
Eggs	Nil	1	Nil	1
Milk	6 oz	6 oz	12 oz	12 oz
Ghee	2 oz	2 oz	$3^1/_2$ oz	$3^1/_2$ oz
Vegetable oil	$1^1/_2$ oz	$1^1/_2$ oz	Nil	Nil

Atta is coarsely ground wheat flour, plus 15% bran *Dhall* is the pigeon pea, *Cajanus indicus* Vegetable oils, which are prepared locally, include simsim oil which is made from millet, groundnut oil, and cottonseed oil, none of which are hydrogenated

The figures for milk in the original table have been altered to conform with the average adult consumption at the present time

The male Indian population of Kenya over the age of 15 therefore includes the following main groups

Gujerati vegetarians (Hindus)	10,000
Gujerati non-vegetarians (Muslims)	6000
Total Gujeratis	16,000
Punjabi vegetarians (Hindus)	5000
Punjabi non-vegetarian Sikhs	3000
Punjabi non-vegetarian Muslims	3000
Total Punjabi non-vegetarians	6000
Total Punjabis	11,000
Total Indians in these groups	27,000

Our series consists of 320 consecutive cases of ischæmic heart-disease seen in Kenya during the past thirteen years, including 170 Gujeratis, 104 Punjabis, and 46 Goans All the diagnoses were confirmed clinically and electrocardiographically by one of us Necropsy in fatal cases was never possible, since Indians in Kenya never allow postmortem examinations on their relatives All were men with the exception of 21 women (18 Indians and 3 Goans)

A comparison between the 153 vegetarian and the 103 non-vegetarian males showed that hypertension was slightly more frequent (30%) amongst vegetarians than non-vegetarians (25%) and that diabetes had approximately the same incidence (13% and 15%) in the two groups The total Gujeratis and total Punjabis displayed almost the same proportions of each disease

The ages of the male patients in the various communities are given in table I, which reveals that the incidence of coronary disease is highest in the sixth decade

The standard daily diets of the main Indian groups [3] are listed in table II According to Adalja,[2] the average consumption of milk and ghee has fallen by about 30% since 1927, partly because more tea, and correspondingly less milk, is taken, and partly because these substances were thought to give protection against malaria and pneumonia before the advances of chemotherapy There has also been a tendency since the end of the late war for a few of the vegetarians to be less strict in their diet, particularly when they go out to meals with members of other communities

The incidence of ischæmic heart-disease in relation to Kenya population in the different groups, is depicted in table III

TABLE III—INCIDENCE OF ISCHÆMIC HEART-DISEASE IN MEN IN RELATION TO MALE POPULATION OVER THE AGE OF 15

—	No of cases	% of total Indian cases	Kenya population (approx)	Population % of total Indians
Gujerati vegetarians	112	44	10,000	37
Gujerati non-veg	45	17	6000	22
Total Gujeratis	157	61	16 000	59
Punjabi vegetarians	41	16	5000	19
Punjabi non-veg Sikhs	32	13	3000	11
Punjabi non-veg Muslims	26	10	3000	11
Total Punjabi non-veg	58	23	6000	22
Total Punjabis	99	39	11,000	41
Total Indians	256		27,000	

For the sake of accurate comparison females have been excluded because they form such a small proportion of the coronary cases and because the sexes of the Sikh community differ in their diet, females being predominantly vegetarian whereas males are usually non-vegetarian Since the *Statistical Abstract* [1] gives no separate figures for population between the ages of 15 and 60, the estimates in this table comprise males over the age of 15

The ratio between percentage incidence of ischæmic heart-disease and percentage of population is almost identical in the total Gujeratis and total Punjabis, the percentage coronary moribidity in each case being closely proportional to that of population, in spite of the fact that the Gujeratis are the lowest and the Punjabis the highest fat consumers These statistics suggest, therefore,

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1 Statistical Abstract, East African Statistical Department, Kenya Unit, 1958
2 Adalja, K V Personal communication, 1959
3 Harvey, D *East Afr med J* 1943, 20, 235

that, as was hinted by Adalja,[4] in the case of Indians in Kenya the ingestion of animal fats is not an important ætiological factor Another point of interest is that the amount of vegetable oils, such as simsim, groundnut, and cottonseed oils, which are not hydrogenated, tends to be consumed in inverse ratio to that of animal fats It thus seems that the Gujerati vegetarians were not protected from coronary occlusion by a high intake of unsaturated fatty acids

Smoking does not seem to be an important factor since Sikhs, who never smoke, show approximately the same incidence of ischæmic heart-disease in relation to their population as the other Punjabis and total Gujeratis, amongst whom smoking is practised by most Indian males over the age of 25

We consider that further research into the comparative incidence of coronary occlusion amongst the various Asian communities in Kenya, analysis of their diets, and counting of their populations might throw more light upon the ætiology of the disease

We wish to express our gratitude to the Hon Dr K V Adalja for his valuable assistance in classifying the various Indian groups and in providing particulars concerning their population and diet We are also grateful to the doctors who referred their cases to us

Nairobi,
Kenya

A D CHARTERS
B P ARYA

HOTELS OR HOSPITALS?

SIR,—I have read Mr Stallworthy's article of Jan 9 with great interest Experience of the operation of convalescent annexes or halfway houses attached to geriatric units supports his suggestion that the provision of these annexes for other medical units would be of value A number of halfway houses have been established by the King Edward's Hospital Fund for London and by the National Corporation for the Care of Old People, and my observations are based on the working of the home attached to the geriatric unit of the Whittington Hospital during the past nine years

The adverse psychological effects of prolonged stay of geriatric patients in the hospital ward are well recognised Apart from apathy and personality deterioration many patients, lacking incentive, become dependent on the services of the nursing staff Whereas what is needed is encouragement for the patient to become independent after the acute phase of his illness has been treated Independence is often more easily achieved in the halfway house than in the hospital ward One of the most important functions of the halfway house is to provide facilities for further rehabilitation and thus shorten the length of stay in hospital The patient with hemiplegia, for example, may have recovered sufficiently in hospital to be able to walk, but because he cannot dress himself or manage stairs he is still dependent on help from others He can learn to perform these activities in the halfway house where a marked improvement in morale and speed of recovery is often noticed as confidence and interest in living are renewed Hemiplegic patients whose recovery was satisfactory spent on the average 7 weeks in the geriatric unit and a further 5 weeks in the halfway house before returning to an independent existence at home.

Another important advantage of the recovery annexe or halfway house is that the patient's physical and mental capabilities can be more easily assessed there than in the hospital ward Thus the patient is not discharged home until it is reasonably certain that he or she is capable of managing at home As a result premature readmission to hospital can be avoided Adams[5] found that with the availability of the beds in Seapark, a recovery home attached to the Belfast Geriatric Unit, the readmission-rate in 1953 fell from its usual level of 12% to 8%

The possible dangers of loss of continuity of care mentioned by Mr Sanford (Jan 23) are not present in the case of the halfway house whose operation I have observed But continued regular visits by the hospital consultant and by the almoner are essential As far as possible the plan for the patient's further care is decided upon before he is transferred from hospital to the annexe The successful operation of halfway houses at present in existence, their undisputed value to geriatric units, and the substantial contribution they make to the recovery of many elderly patients indicate the need for similar homes attached to other medical units which are treating an ever-increasing proportion of patients in the older age-groups

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A N EXTON-SMITH

FIBRINOLYTIC ACTIVITY OF BLOOD IN INTERMITTENT CLAUDICATION

SIR,—We were interested to read Dr Nestel's paper of Sept 19, in which he says that deficient fibrinolysis has been previously demonstrated only in acute episodes, as in coronary occlusion In this clinic, the fibrinolytic activity was measured in thromboangiitis obliterans, arteriosclerosis obliterans, and atherosclerosis

Fibrinolysis in the euglobulins was depressed in 6 out of 24 cases of arteriosclerosis obliterans and in 4 out of 21 cases of thromboangiitis obliterans In 100 patients with atherosclerosis there was a tendency to deficient fibrinolysis in the euglobulins and a statistically important prolongation of fibrinolysis time of total plasma activated with streptokinase No changes in plasminogen activity were found A possible relation of these findings to the antifibrinolytic activity was considered

The results[1] were given to the XIX Congress of the Polish Internists Association in Poznan in September, 1957, and to the XX Congress in Gdansk last September The problem of fibrinolysis in atherosclerosis was also discussed by other Polish authors (E Szczeklik et al and H W Gajewski)

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WINCENTY CZARNIECKI

ANABOLIC STEROIDS AND RADIATION DAMAGE

SIR,—Szold et al[2] and Feher et al[3] demonstrated significantly higher survival-rates in nephrectomised uræmic animals treated with an anabolic agent, 19-nor-androstenolone phenylpropionate ('Durabolin') than in controls The uræmic state has many similarities to acute radiation sickness, and the idea was thus raised that acute radiation damage might be retarded or prevented by anabolic agents

Adult male rats were given a total-body dose of 1000r (180 kV, 6 mA, 2 5 Al filter, 50 cm. focus-skin distance, the dose controlled with a Siemens-Universal dosimeter) The animals to be protected were given, at the onset daily, later on every second day, 0 5 mg of 19-norandrostenolone phenylpropionate, and the controls received the same amount of physiological saline

From the second day after irradiation the clinical appearance of the animals became very similar to that of rats with arenal uræmia, with the difference that the symptoms of the protected animals were significantly less The protected animals were fresher, responded better to external stimuli, were curious, and had a better appetite Before they died all became restless and dragged their hind limbs which were subject to convulsive spasms

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[4] Adalja K V Kenya Faculty of the College of General Practitioners, London Oct 4, 1958

[5] Adams G F *Lancet*, 1954, ii 486

[1] *Polskie Archiwum Medycyny Wewnętrznej*, 1958 12, 1569

[2] Szold E Szendroi, Z, Weisz P, Pinter, I, Desi, I, Kadas T *Lancet*, 1959, i 368

[3] Feher I Dési I Szold, E *Magyar Tudományos Akadémia V oszt Közleményei*, 1958, 9, no 3-4

After the third day both groups showed a distinct reduction in temperature and weight, and these changes were accompanied by diarrhœa for two or three days

The five series (taking into consideration the first 10 days) showed a significant 40% difference in survival in favour of the protected animals

By the fortieth day the protected animals and the controls showed practically no difference in survival A protected and a control animal of two series were killed and their organs examined Histologically the testicles of the controls showed severe degenerative changes, whereas in the protected animals there were well-recognisable testicular ducts, good nuclear staining, and even spermatogenesis here and there

Our observations so far and the difference in the histological appearance of the testes give reason to extend these experiments on a larger scale

E Szold
B Gimes
B Erdos

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A NEW STEROID IN THE URINE IN NEPHROSIS

Sir,—In the course of steroid estimations a new reducing substance which behaves chromatographically like a corticosteroid has been found in the urine of untreated nephrotic patients

After 24 hours of mild acid hydrolysis at pH 1, the urines of 8 nephrotic children were extracted with chloroform After extraction the urines were incubated at pH 4 5 with 25 units per ml of calf-spleen glucuronidase for 48 hours, and again extracted with chloroform To purify them, the fractions were partitioned between benzene and water The materials from the watery phase were then run on paper in Bush's C chromatographic system [1] at room temperature

On spraying the paper with alkaline tetrazolium-blue solution, we found a reducing substance with R_f value of 0 58 (corresponding R_f values are hydrocortisone 0 3, cortisone 0 44, 11-desoxy-17-hydroxycorticosterone 0 65, corticosterone 0 75) The substance eluted from the paper was then acetylated and rerun in a system of hexan/benzene/methanol/water 4 1 4 1 The R_f value of the acetate was 0 29 (corresponding values hydrocortisone acetate 0 05, cortisone acetate 0 11, 11-desoxy-17-hydroxycorticosterone acetate 0 08, corticosterone acetate 0 07, aldosterone-21-monoacetate 0 07, aldosterone-18,21-diacetate 0 21)

The substance gives a positive soda-fluorescence test indicating the presence of a Δ^4-3-keto group, and it is Porter-Silber negative, therefore does not contain a hydroxyl group on C_{17} The prompt reaction to tetrazolium-blue suggests the presence of a ketol rather than a glycol side-chain, and the relatively high R_f value of the acetate suggests a diacetate form The substance is not identical with Nowaczynski's compound III [2] Its identity with Pasqualini's compound has not been investigated [3]

This steroid could not be demonstrated in nephrotic urine by only mild acid hydrolysis, nor could it be seen in the urine of healthy children even though it was subjected to hydrolysis with glucuronidase After suppression of the secretory activity of the patients' adrenals with prednisone or prednisolone, the substance disappeared from the urine in 4 cases studied

The purpose of our future investigations will be a more precise identification of this steroid and observation of the changes in excretion of the substance at different stages of this and other diseases

J Csordás
P Jobst
P Cholnoky

Children's Clinic,
University of Pécs, Hungary

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1 Bush, I E *Biochem J* 1952, 50, 370
2 Nowaczynski, W Steyermark, P R , Koiw, E , Genest, J , Jones, R W *Canad J Biochem* 1956, 34, 1023
3 Pasqualini J *C R Acad Sci , Paris*, 1958, 247, 1061

PREVENTION OF MIGRAINE IN CHILDRE BY PROCHLORPERAZINE

Dr Nevil Leyton writes

" Contrary to what Professor Illingworth and Dr imply in their article of Jan 16, I have never made any that ' Stemetil ' alone is particularly useful in the prevent migraine Indeed, I said [1] ' many patients whom I have t with it have either been unaffected or their headaches worse, although I am glad to say that some have bene The conclusions Professor Illingworth and Dr Harvey reached simply confirm my own

" It has always been my opinion that no one schem certainly no compound, will ever be of universal use i venting attacks of migraine The compound which I found most consistently of use, particularly when assist others, is chorionic gonadotrophin [2] "

Parliament

The Scottish Mental Health Bill

In Scotland the law relating to mental health differs in ways from English practice Its revision was considered b Russell Committee which reported in 1946 [3] and a white- setting out proposals for its amendments was publish 1955 [4] Action was deferred until the English Royal Con sion should report, and the Secretary of State for Scotland invited the Scottish Health Services Council to conside application of the Commission's main recommendatio Scotland The council has published two reports [5] fron committee which they set up for this purpose The M Health (Scotland) Bill, which has been prepared against background, will have its second reading soon after Parlia reassembles Its main provisions are described in a w paper [6] published by the Department of Health for Scotl

The Bill accepts most of the recommendations of the lish Royal Commission—notably, that mental patients sh have access to care and treatment without formality, that c pulsion should be reduced to a minimum, and that community mental-health services should be developed

In three important respects, however, the Scottish departs from the English legislative pattern Througl " mental disorder " is used as a general term to cover me illness and mental deficiency and these are the only categ mentioned in the Bill

The Bill dissolves the General Board of Control for S land, but sets up in its place a Mental Welfare Board w will continue to carry out the old board's protective funct by investigating complaints and visiting patients in hospita under guardianship The board will have not fewer 5 members and not more than 7, of whom at least 2 must doctors

The Bill also retains the services of the sheriff, a traditio Scottish legal officer who has no exact English counterp Thus the sheriff must approve applications for compuls admission (which must be signed by two doctors) The patie or his nearest relative, has also the right of appeal to sheriff against continued detention This procedure take the place of the new appeal tribunals to be set up un the English Bill

The Scottish Bill places a specific duty (not provided und the present law) on the doctor in charge of the patient to d charge him if he no longer needs to be detained A simil duty is also placed on the new Mental Welfare Board. (T nearest relative, or the hospital board or local authority co cerned, may also discharge a patient) Courts will for the fi time be given the power to remand in hospital instead of custody people who seem to be mentally disordered

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1 Leyton N *Lancet* 1957, ii, 242
2 Leyton, N *ibid* 1942, i, 448
3 See *ibid* 1946, ii 166
4 *ibid* 1955, ii, 1983
5 *ibid* 1958, ii, 741
6 H M Stationery Office 1960 Pp 15 1s

Notes and News

WORLD HEALTH ORGANISATION

ON Jan. 19 the Executive Board of W H O met in Geneva under the chairmanship of Prof E Aujaleu, director-general of public health, France By the end of November about $1^{1}/_{2}$ million dollars had been contributed to W H O 's malaria radication campaign A further $8^{1}/_{2}$ million dollars is needed o finance W H O 's malaria commitments up to the end of 1961

The canton of Geneva has now designated the property which it will place at the disposal of W H O for its new building, while the Swiss Parliament has authorised an interest-free oan to W H O of 20 million Swiss francs, repayable in wenty annuities

The regular working budget of the Organisation proposed for 1961 is $18^{1}/_{2}$ million dollars

HINCHLIFFE RECOMMENDATIONS

THE Ministry of Health has been considering the report of the Hinchliffe Committee, and, with the agreement of the General Medical Services Committee, has commended to general practitioners (ECN 319) the recommendation that they should restrict the quantities of drugs they prescribe The Committee suggested that normally, except for chronic patients, the amount of drugs to be ordered on one prescription should not exceed one week's supply Other recommendations which the Ministry commends are that official titles should be used on prescriptions in preference to proprietary names, and that practitioners should avoid prescribing unnecessarily elaborate preparations The Committee's suggestion that new drugs should not be used in the National Health Service until they have undergone independent clinical trials is under consideration Meantime doctors are asked, until the results of trials are known, to prescribe new drugs only if they are sure that existing drugs have failed It has been agreed with the professional bodies to produce a looseleaf handbook including much of the British *National Formulary* and facts about comparative costs of standard and proprietary preparations, and it is hoped to circulate copies to general practitioners soon The value of pre- and post-graduate training and education in prescribing is also stressed, especially arrangements for seconding medical students to general practitioners, refresher courses for practitioners, and the trainee practitioner scheme

MALNUTRITION IN AFRICA

AT Dar-es-Salaam on Jan. 13, opening a scientific conference on the Origin and Effects of Malnutrition in Man and Animals, Sir Richard Turnbull, the Governor of Tanganyika, gave highest priority to studies connected with infant mortality and infant malnutrition in the hope of removing " those heavy handicaps of stunted physical growth and impaired intellectual development which so often result from early deficiencies in diet " Enormous areas of Tanganyika, he said, were infested with tsetse and as a result stock-farming in about two-thirds of the country was impossible The people living in and behind the fly areas suffered from a general protein deficiency, and he wanted to know whether this could be made good from vegetable sources alone and without reliance upon milk in any form

" I feel that if we are to find a solution to this problem and not just a palliative, it must come from local resources, we cannot afford to be dependent on a supply of milk or some kind of animal protein concentrate from outside as a supplement to the diet '

Prof B S Platt, in his presidential address, said that twenty years ago there was much talk of the " lazy African "—often coupled with talk about the need for incentives for him to better his lot.

' I have always tended to associate indolence with ill-health When I first visited East Africa in 1938, I had fresh in my mind the contrast between the listless and apathetic, poorly fed apprentices in small factories in Shanghai and the noisy, mischievous and high-spirited ones who were well fed from a kitchen run under my supervision, and I found a similar contrast between groups of well and badly fed labourers in the goldfields in Tanganyika "

The morphological changes found in the central nervous system in animals in experimental malnutrition might, Professor Platt thought, have some relevance to certain mental disturbances in malnourished human beings

HOSPITAL MICROCOSM

MANY doctors who read the *Graver Tribe* were left with a feeling that they had involuntarily acquired a second medical school Those who have been awaiting further news about St Chad's will turn to Edward Candy's new book [1] to catch up with the gossip of what must surely be the wittiest and most civilised hospital in London Nor will they be disappointed Within a few pages they will be *au fait* with the tussle for the old eye and tubercle wards on the top floor of the surgical block, alert to find out whether Clayton will successfully commandeer them for his burns unit or whether they will be given to Branksome as a temporary surgical home till his new unit is built

One of the reasons why we are so much absorbed by St Chad's is that the staff and their womenfolk, the patients and their relatives, show the same maddening mixture of good and bad, strength and weakness, generosity and meanness as our own friends or even ourselves This time Mr Candy has been content to avoid the interruption of near-melodrama and leaves us to follow the much more exciting manœuvre in committee, exchange at the hospital dance, or row in out-patients But the everyday never lapses into the trivial, for he recognises the universal issues behind the humdrum, respects diverse but sincere principles, and offers his own implicit, though never explicit, judgments

University of London

The following degrees have been awarded

M D—John Burston A M Dawson, P J Koblenzer, A C K Lawrence, Ian Macdonald, J D Pryce

Ph D (in the faculty of medicine)—Krishna Rao Voommaji Rao Ghorpade

University of Aberdeen

Dr I B Porteous has been appointed a lecturer in pathology

University of Glasgow

The Bellahouston medals for 1959 have been awarded to W A J Crane, James Crooks, and A J S McFadzean

On Jan 16 the degrees of M B, CH B were conferred on Yuill Black (in absentia)

Monash University

Dr A J Marshall has been appointed professor of biology at this new university in Victoria, Australia

University College Hospital

Prof Montague Maizels will give the Sydney Ringer lecture at the Medical School, University Street, London, W C 1, on Tuesday, March 15, at 4 30 P M He will speak on salt and water balance in cells

World Health Day

The theme chosen for World Health Day for 1960 is Malaria Eradication—a World Challenge It will be held as usual on April 7

Partnership in Preventive Medicine

The Society of Medical Officers of Health and the College of General Practitioners will hold a postgraduate conference on July 16 and 17, at the medical school, University of Birmingham Further particulars will be given later

North of England Obstetrical and Gynæcological Society

The following officers have been elected for 1960

President, Prof T N A Jeffcoate, *vice-presidents*, Mr J B Farquhar, Sir Arthur Gemmell, Miss E M Mills, Mr J M King, Mr J A Hadley, *hon treasurer*, Mr T B FitzGerald, *hon general secretary*, Mr H V Corbett, *hon reporting secretary*, Miss U M Lister

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[1] A Lady s Hand By EDWARD CANDY London Gollancz 1959 Pp 192 13*s* 6*d*

International Conference on Medical Electronics

This conference will be held at Olympia, London, from July 21 to 27 Further particulars may be had from the conference secretariat, Institution of Electrical Engineers, Savoy Place, W C 2

European Congress on Aviation Medicine

This congress will be held in London from Aug 29 to Sept 2 Further particulars may be had from the congress secretary, c/o British European Airways, Central Medical Clinic, London Airport (N), Hounslow, Middlesex

Rehabilitation of the Amputee

A course for orthopædic consultants and senior registrars will be held from March 28 to April 1 at the Limb Fitting Centre, Queen Mary's Hospital, Roehampton, London, S W 15 Applications should be sent to the Principal Medical Officer, Artificial Limbs and Appliances (Med 5 PL) at the same address

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Prof A D Macdonald, president of the British section of the Franco-British Pharmaceutical Commission, has been appointed an officer of the Ordre de la Santé Publique by the French Minister of Health

The Yorkshire Society of Anæsthetists will hold their annual general meeting on Wednesday, Feb 10, at 8 30 P M at the General Infirmary at Leeds Dr W J Finnie will give his presidential address on the training and distribution of anæsthetists

The Group for Representation of the Views of Clinical Psychiatrists will meet on Tuesday, Feb 16, at 5 30 P M, at Tavistock House North, London, W C 1 The secretary of this group is Dr B C Gilsenan, Shenley Hospital, near St Albans, Herts

The National Institutes of Health have published a bibliography (*Publ Hlth Serv Publ* no 669) of papers published in English during 1952–58 about the effect on the offspring of the following disorders in the mother infectious diseases, diabetes, thyroid dysfunction, myasthenia gravis, lupus erythematosus, sickle-cell disease, thrombocytopenic purpura, leukæmia, drug addiction, and drug administration Statistical studies of perinatal morbidity and mortality are also included A limited number of copies are available from the library of the Institutes, Bethesda 14, Maryland Additional copies may be purchased from the Government Printing Office, Washington 25, D C (15 cents per copy)

Boarding-out Schemes for Elderly People —Copies of this booklet (1*s* 6*d*) may be had from the National Council of Social Service (26, Bedford Square, London, W C 1) It offers advice on how to run a boarding-out scheme and includes a brief survey of information drawn from existing schemes sponsored by voluntary bodies and local authorities

'Versenate', mentioned in the paper by Dr Miller and Dr Smith (Jan 2), is a trade mark of the Dow Chemical Co, and Riker Laboratories Ltd are registered users

Appointments

CHYNOWETH, ALAN, M R C S assistant M O H and school M O, Derbyshire
EUSTACE, MURIEL M, L R C P I school M O, Co Durham
HOWARTH, BESSIE, M B Lpool assistant divisional M O, Lancashire (Golbourne area)
JOHNSON, WILLIAM, M R C S senior M O for mental health, Staffordshire
LINFOOT, C W, M B Durh senior casualty officer (medical), Newcastle upon Tyne group of hospitals
MURPHY, M I, M B, D P H school M O and assistant M O H, Leicester
PEPPER, M, M B Lond school M O and assistant M O H, Leicester

East Anglian Regional Hospital Board

BOYD, R V, M B Lond, D C H registrar in geriatrics, Ipswich and East Suffolk hospital group
DEW-JONES, J A, M R C S senior registrar in psychiatry, St Andrew's Hospital Norwich
HARRIS, W G, M B Lond surgical registrar, Ipswich and East Suffolk Hospital
HODGSON, O E F, M B Cantab, D P M consultant psychiatrist, Fulbourn and Addenbrooke's Hospitals
JADHAV N A, M B Mysore, M R C P E medical registrar, North Cambridgeshire and Clarkson Hospitals, Wisbech
JENKINSON JANE G, M B Lond, D C H pædiatric registrar, Ipswich and East Suffolk Hospital
LAWRENCE G A, M B Lond, F R C S E surgical registrar, Norfolk and Norwich Hospital
SINGH, P, M B Lucknow, M R C P medical registrar, West Suffolk General Hospital
SKORBINSKI, A W, M B Cape Town surgical registrar, Peterborough Memorial Hospital
SMITH, B A M, M B Leeds, D C H pædiatric registrar, Peterborough group of hospitals
SUKUMAR, I P M B Madras medical registrar, Papworth Hospital

Diary of the Week

JAN 31 TO FEB 6

Monday, 1st

GUY'S HOSPITAL, S E 1
5 30 P M Dr Oliver Garrod, Dr I H Mills Aldosterone Metabolism
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P M Mr N W Please Elements of Statistical Methods

Tuesday, 2nd

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Dr L G Norman Medical Aspects of the Prevention of Road Accidents (*First of two Milroy lectures*)
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 P M Mr A H C Ratliff Fractures of the Femoral Neck in Children (Hunterian lecture)
UNIVERSITY OF LONDON
5 30 P M (Middlesex Hospital Medical School, Mortimer Street, W 1) Dr Honor B Fell Experimental Transformation of Cells
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 30 P.M *Pathology and Medicine* Prof Alan Kekwick, Prof J W S Blacklock, Dr R R Wilson The Pathologist and the Patient
8 30 P M *Orthopædics* Mr David Trevor Treatment of Congenital Dysplasia of the Hip in Older Children (Presidential address)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr Paul Fourman Magnesium Metabolism in Man
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Mr J G Dumoulin Fœtal Distress
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Dr H C Grant Pathology of the Dementias
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr P J Hare Coccal Infections
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Dr Denis Hill E E G Diagnosis of the Epileptogenic Focus
UNIVERSITY OF ST ANDREWS
5 P M (Queen's College, Dundee) Prof Adam Patrick Herpes Zoster

Wednesday, 3rd

ROYAL SOCIETY OF MEDICINE
5 15 P M *History of Medicine* Dr J F E Bloss History of Sleeping Sickness in the Sudan
8 P M *Surgery* Mr Rodney Maingot Surgical Aspects of Non-malignant Stricture of the Bile Duct with Special Reference to Postoperative Strictures (Presidential address)
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Rare Tumours of the Skin
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr W E Lloyd Observations on Round Foci
ASSURANCE MEDICAL SOCIETY
5 P M (11, Chandos Street, W 1) Discussion Doubtful Cases
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P M (18, Nicolson Street, Edinburgh) Prof G L Montgomery Observations on the Pathology of the Myocardium
UNIVERSITY OF ST ANDREWS
2.30 P M (Queen's College, Dundee) Dr F L Mitchell, Prof R B Hunter Methods of Investigation of Adrenal Cortical Function.

Thursday, 4th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P M Dr Norman Medical Aspects of the Prevention of Road Accidents (Last of two Milroy lectures)
ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 30 P M Prof T Pomfret Kilner Plastic Surgery of the Upper Jaw
ROYAL SOCIETY OF MEDICINE
8 P M *Neurology* Mr D W C Northfield, Dr G F Swann, Dr James Bull Development in Contrast Radiography
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P M (London School of Hygiene and Tropical Medicine) Prof E B Verney Aspects of the Renal Excretion of Water and Electrolytes
UNIVERSITY COLLEGE, Gower Street, W 1
5 P M Dr Elizabeth Work The Mucopeptides of Bacterial Cell Walls (First of two lectures)
UNIVERSITY OF ST ANDREWS
5 P.M (Queen's College, Dundee) Dr E M McGirr Development of Knowledge of the Ætiology of Goitre

Friday, 5th

UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine) Prof Heinrich Pette (Hamburg) Experimental Demyelinating Diseases and Their Implications in Neurological Diseases of Man
ROYAL SOCIETY OF MEDICINE
2 30 P M *Laryngology* Mr Ivor Frew, Dr E A Cooper Tracheostomy and Controlled Respiration
5.30 P M *Anæsthetics* Dr John Bullough Obstetric Analgesia Based on Pethidine/Antagonist Mixtures
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Sir Russell Brock Basic Principles in Cardiac Surgery
4 P M Mr Please Elements of Statistical Methods
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
3 30 P M Mr G H Howells Cancer of the Larynx
INSTITUTE OF NEUROLOGY National Hospital, Queen Square, W C 1
4 P M Dr J Purdon Martin Observations on Involuntary Movements and Tremor

Saturday, 6th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
NOON Dr Roger Maspetiol (Paris) Factors of Success in Tympanoplasty
MIDLAND THORACIC SOCIETY
3 P M (36, Harborne Road, Edgbaston Birmingham, 15) Prof W Melville Arnott Management of Cardiac Failure

The Lancet · Saturday 6 February 1960

EARLY TREATMENT OF STOVE-IN CHEST *

N R Barrett
M Chir Cantab, F R.C S
SURGEON, ST THOMAS'S HOSPITAL, LONDON, S.E.1,
AND BROMPTON HOSPITAL, LONDON, S W 3

A " stove-in chest " results from multiple rib fractures or from disruption of the costosternal cartilages, it is often complicated by other injuries, but its peculiar feature is paradoxical movement of the chest wall at the site of the fractures

Paradoxical movement causes asymmetrical expansion and contraction of the thoracic cage, and this, in its turn, produces inadequate absorption of oxygen and elimination of carbon dioxide from the alveoli These patients die from " respiratory failure " and not because a few bones have been broken The purpose of this paper is to underline the fact that some who now die can be saved by simple treatments

The perfection of fast touring cars and the construction of modern motorways have made these injuries common, but few surgeons are, as yet, experienced in the emergency treatments that may be vital The victim is hurried away to the nearest hospital where he dies or survives almost irrespective of the things that may be done for the chest injury A thoracic surgeon seldom sees the patient unless he survives for at least 48 hours, and so it behoves those responsible for the reception of accident cases to acquaint themselves with measures that are easy and effective.

Nature of the Injury

This type of chest injury occurs when the hoops composed of vertebral column, ribs, cartilages, and sternum are suddenly compressed The direction of the forces that fracture the ribs is often an outward burst at the weakest parts of the hoops—as opposed to the local inward thrust of direct violence Paradoxical movement can be recognised by looking at the chest wall as the patient breathes or, if this is not practicable, by palpation.

The critical extent of such an injury varies from patient to patient, the young tolerate more than the aged, and every moment the patient survives is time gained in his favour If an injured person reaches a hospital alive respiratory failure should still be reversible, but minutes count.

An acquaintance with the management of thoraco-abdominal injuries sustained in war is not an adequate background for this work. The complications of stove-in chest are different. The importance of peritonitis and intra-abdominal hæmorrhage is eclipsed by concomitant head injuries and fractures of the long bones, vertebræ, and pelvis, and by complicating factors in the chest itself, as well as distension of the stomach and ileus

Patients with multiple injuries, including " a stove-in chest ", often die without obvious cause Hæmorrhage has been stemmed, transfusions have been given to combat shock, and ample morphine has relieved the sharp edge of the pain. The sedated patient lies quietly in bed and his shallow paradoxical respiratory movements escape critical notice But death steps in suddenly, peacefully, naturally —and unnecessarily

The accurate assessment of everything that contributes to this outcome is difficult, but, considering chest-wall injuries alone, the following points are relevant

Paradoxical movement of the chest wall, uncomplicated by any serious intrathoracic injury, can be fatal It was the principal cause of death in the early days of thoracoplasty The harm it does is comparable to that of open pneumothorax, but of lesser degree in most cases The flail area is sucked in as the chest expands, and blown out during expiration The result is that some of the air that should be exchanged by passing in and out of the lungs, is shunted from one side of the chest, or from one part of the lung, to another In severe cases this movement of air displaces the mediastinum to and fro during respiration, and this used to be called " pendulum movement " It was considered to be dangerous because it was said to hinder blood returning to the right atrium, it is dangerous because it produces asphyxia

It has been shown by bronchospirometry that a single, simple, rib fracture causes, reflexly, a measurable reduction of gas exchange in the lungs This is due to a partial shut-down in the pulmonary vessels supplying the underlying lung It is not of clinical importance if the patient's reserve of compensation is not seriously affected But in severe injuries the resultant reflex pulmonary hypertension can eliminate gas exchange completely in all or part of a lung, and this happens even though the respiratory movements continue

Pain upon respiration adds to the oxygen deficit by reducing the excursion of the chest wall and so by diminishing the volume of tidal air Cough is suppressed because it hurts, and reflex spasm of the bronchial muscles contracts the lumen of the respiratory passages

The patient has increasing difficulty in getting rid of bronchial and alveolar exudates, and the development of a " wet lung " is Nature's last cry

Why secretions first accumulate in the bronchial tree is not clear But it is certain that in the early hours after serious accident pulmonary œdema occurs, and this has been explained in several ways Possibly the shut-down in the pulmonary vessels underlying an injured chest wall could cause anoxia and œdema of the affected alveoli Alternatively the sudden diversion of a large proportion of the cardiac output might initiate hyperkinetic œdema in the sound lung Cardiac failure and cerebral injuries may also play a part, and over-transfusion is a risk. Be these things as they may, the casualty surgeon must know that pulmonary œdema and retained bronchial secretions can kill within an hour of an accident, even though the lung itself has not been directly wounded Moreover, the presence of bloodstained, watery expectoration is not necessarily due to a lung wound.

If a patient survives the initial risks of early pulmonary œdema, the retained secretions may become infected during convalescence and " bronchopneumonia " sets in. This should be preventable

In addition to ventilatory difficulties the position is frequently aggravated by a lung wound, by intrapulmonary or intrapleural hæmorrhage or pneumothorax, by hernia if the diaphragm has been ruptured, or by acute dilatation of the stomach Any, or all, of these can make breathing impossible

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* An address to the Society of Thoracic Surgeons of Great Britain and Ireland, Newcastle upon Tyne, November, 1959

7119

A major chest injury causes temporary restriction of the diaphragmatic excursions on the affected side The dome of the diaphragm is always high

A patient who has a " stove-in chest " and who reaches hospital alive is living on his pulmonary reserve He now faces the additional hazard of being given morphine or other respiratory depressants

The harmful effects of anoxia are cumulative and ultimately become irreversible

Treatment

In the care of a patient with multiple injuries including a " stove-in chest ", attention cannot be confined to the chest injury, but in the first few hours treatment of this injury takes precedence over everything except primary hæmorrhage

As a whole such treatment falls into three periods during which the aims are different Immediately after the accident, and during the next 48 hours, *the object is to correct inadequacies in the act of respiration* In those who survive, pulmonary infections must be forestalled, and total expansion of the lung on the affected side achieved and maintained During convalescence normal movements of the chest wall and diaphragm must be regained

The advice that follows concerns the emergency treatment only

When a patient who has a " stove-in chest " and respiratory difficulty is admitted, give an anæsthetic, pass a cuffed intratracheal tube, and start controlled respiration The anæsthetic is necessary to allow respiration to be controlled—and it is the latter that is important, not the former Respiratory efforts by the patient can be abolished by producing alkalotic apnœa, by giving paralysing drugs, or using a combination of both Intubation and controlled respiration saves life and has the additional advantage of enabling secretions to be sucked out of the air passages as often as they accumulate

Experience in the treatment of recently wounded people during the late war, and particularly with young and otherwise healthy adults, showed that the critical state in which they were admitted to hospital was often due to inefficient respiration As soon as the anæsthetist took over control of the act of breathing the clinical state improved, and, if the surgeon could then remedy the anatomical defects, so that spontaneous respiration could be resumed, the " come-back " was rapid and simple

Once the patient has been anæsthetised in the outpatient department, the other injuries can be examined and a plan of campaign adopted This is the moment to decide whether early operation of any type is necessary or not

As far as the chest wall is concerned, determine the extent and position of the unstable areas, and examine the patient to discover other complications If the anæsthetist, giving controlled respiration, cannot achieve easy movements on the affected side, the assumption should be that there is an intrathoracic complication The usual reason why the affected lung cannot be inflated easily is that it is artificially restricted by pneumothorax, tension pneumothorax, blood in the pleural cavity, gastric dilatation, or diaphragmatic hernia

It is not easy to be certain about any of these things clinically, and it may not be safe at this time to sit the patient up for an X-ray of the chest (a film taken in the recumbent position is confusing), but the following details may help Observe the position of the apex beat, and remember that if breath sounds can be heard anteriorly, in the recumbent patient, an important pneumothorax is not present Hæmothorax is particularly difficult to diagnose because, at this stage, the blood moves in the pleural cavity according to the position of the patient (" shifting dullness ") Thus, lying down, the lung floats forward on the blood in the paravertebral gutter and breath sounds are heard over the front of the chest, conversely when the patient sits forwards there are breath sounds at the back. For this reason a hæmothorax of several pints can be missed, unless the patient is examined, recumbent, with a flat stethoscope slipped in between the chest and the bed The only way of diagnosing acute dilation of the stomach or diaphragmatic hernia at this stage is by an appropriate X-ray

If the patient has, in addition to a stove-in chest, a hæmothorax, *put an intercostal catheter into one or both pleural cavities* and connect these to water-seal drainage bottles The usual causes of traumatic hæmothorax are bleeding from the chest wall and, more rarely, from the lung, but in these days of rapid deceleration accidents rupture of the intima and media of the aorta is not uncommon In such cases a false aortic aneurysm develops with oozing into the pleural cavity, they may live for as long as two months before the aneurysm bursts If there is pneumothorax or tension pneumothorax, insert a small polyethylene tube, using a hydrocœle trocar, into the top of the affected pleural cavity through the second or third interspace anteriorly, connect the tube to a sealed drainage or suction apparatus These emergency safety-valves can be maintained for two or three days without risk of intrathoracic suppuration, by this time definitive treatment will have been given and the tubes will have been replaced, or taken out There is no merit in tubes that are blocked by clots in the lumen or by kinks in the dressings If a pneumothorax or tension pneumothorax persists in spite of adequate continuous suction, rupture of a main bronchus should be suspected and, if present, treated by thoracotomy without delay

Cardiac tamponade is a rare complication of stove-in chest, but if it be suspected the pericardium should be tapped by passing a long needle from the side of the xiphisternum upwards and backwards for a distance of about 10 cm Blood that restricts the movements of the heart accumulates behind the ventricles and can be aspirated without difficulty A misdirected tap is not dangerous because the needle approaches the least vascular part of the heart—that is, the apex

The above measures may be necessary in the accident department They are simple and, once completed, a proper assessment of the other injuries can be made without danger to the patient The emergency time is over

The surgeon must now decide how efficient respiration is to be maintained, and this decision is difficult It will be obvious that if other treatments, such as traction for a fractured femur, are to be used, the management of the chest *from now onwards* must be unobtrusive and effective

The first decision to take is whether the flail chest wall should be stabilised by local treatment, and several alternatives are available

The first of these is to pad and strap the affected area Do not do this, for these reasons Strapping is easy to apply but difficult and painful to take off, the man who puts it on seldom has to take it off and, consequently, he does not shave the skin It is a wasteful way of preventing paradox because, to be effective, the strapping must immobilise a much wider area than has been damaged It may augment the respiratory inefficiency by fixing parts of the chest wall that would otherwise move effectively. It makes X-rays difficult to interpret, and it hinders aspirations of the pleural cavity. It has no merit except ease of application.

There are a variety of minor operations that can be done under local anæsthesia and help some forms of paradox. The sternum can be elevated and held by traction applied to a cuphook screwed into the body of the bone and attached, over a pulley, to an appropriate weight. This can be effective.

The fractured ribs can be elevated and held by inserting several towel clips through the skin and around the mobile parts of the ribs, and applying traction in an outward direction.

Two or more Steinmann pins can be inserted under local anæsthesia, and through tenotome punctures in the skin, so that they cover the defect in a criss-cross fashion like boards nailed across a broken window. The pins rest upon the intact ribs and should be deep to the sheet muscles of the shoulder girdle.

These are temporary expedients, and are seldom used because they are not sufficiently good. But some surgeons are convinced of the necessity to stabilise the chest wall and they advocate open operation for the purpose.

To succeed in such a treatment it is necessary to elevate a wide flap of skin and muscles in the affected area and, having laid the fractures bare, to fix all the broken ribs—fore and aft—so that absolute stability is achieved. To do this one must use intramedullary pegs or wire the fragments in two planes. The operation is not difficult, but it takes time. Once completed there are no external splints or traction appliances to complicate treatment, and the intrathoracic injuries have been accurately assessed at the same time by opening the pleura and examining the thoracic viscera. An operation of this type eliminates paradoxical movement once and for all, and it prevents late persistent deformity of the thorax. It is true that, if it is not done, the late result of a stove-in chest may look like a lateral thoracoplasty and carry the attendant limitation of respiratory function in after-life. Many successes have been reported.

But, in general, these operations are seldom used, and for these reasons. They take time and add to the shock of the existing injuries. It requires mature judgment to balance the possible benefits against the trauma of the additional manipulations, and the problem of how to control bronchial secretions remains. Fortunately alternative treatments are available.

Whenever paradoxical respiration is so severe that it must be controlled, a tracheostomy should be done. Borrie says "the time to do a tracheostomy is when considering whether or not it should be done."

The operation is best done whilst the patient is under the anæsthetic given on admission, and whilst the anæsthetist's cuffed tube is in the trachea. It is simple and accurate to cut down upon a trachea splinted in this way, and to insert a plastic tracheostomy tube on which there is distensible balloon. The balloon need not be inflated, or used, until the result of tracheostomy has been assessed.

The benefits of tracheostomy are that, by diminishing dead space, the patient need not breathe so deeply to ventilate, secretions can be sucked out, oxygen can be given as occasion demands, and obstruction from paralysis of the tongue is eliminated. And mechanical respiration can be started if necessary.

Ingravescent surgical emphysema is a distressing complication of chest injuries. In general it signifies that the lung has been ruptured in one or more places, or it complicates an open pneumothorax that has sealed off, coughing then injects the air, trapped in the pleural space, into the subcutaneous tissues of the chest wall or into the mediastinum and the neck. A tracheostomy controls, prevents, and eliminates surgical emphysema.

It is an unexpected but commonly observed fact that by doing a tracheostomy, and nothing more, the problems of inefficient respiration are solved in many cases. This is particularly true in elderly or bronchitic subjects.

When repeated toilet of the air-passages, by catheter suction is used, *sterile* catheters must be available for the purpose. If this precaution is not taken the patient will probably be given staphylococcal pneumonia, or may acquire an equally intractable organism. This type of complication can determine the issue.

If tracheostomy by itself fails to control the harmful effects of paradoxical movement, or if other complications, such as coma due to an associated head injury, demand more definite measures to ensure efficient respiration, the balloon on the intratracheal tube can be inflated, and the patient connected to a breathing-machine. If this decision has been taken the outlook is serious but not by any means hopeless. There are few circumstances, excluding severe lung or vascular injuries, in which efficient respiration cannot be continued for as long as may be necessary. These patients can be kept alive. But prolonged controlled artificial respiration is not to be lightly pursued by all and sundry, and at this stage the patient should probably be transferred to a unit that specialises in this work. If necessary artificial respiration can be continued in the ambulance whilst the patient is transferred to a respiratory unit, using the hand bellows that are now available.

After tracheostomy, or other definitive treatments, steps must be taken to alleviate pain. The danger of giving morphine, or its derivatives, is stressed by almost everybody who has treated these patients. It depresses cough, encourages retention of bronchial secretions, and favours the development of septic pneumonia. The best alternative is to inject local anæsthesia into the vicinity of the fractures. A single injection may not be enough, but the effects often last longer than one expects. If chest-wall pain continues, a small polyethylene catheter can be introduced into the traumatised area and through this small but adequate amounts of local anæsthetic and antibiotic can be instilled as necessary.

Conclusions

The immediate procedures advocated in this paper and purporting to control the dangerous effects of "stove-in chest" are simple.

The battle that must be won during the first few hours, and the position that must be held for subsequent days or weeks, is against anoxia and carbon-dioxide retention.

Strapping the chest wall, morphine, and barbiturate sedatives are contraindicated. The use of "Drinker type" respirators is bad because they compress the flail chest wall.

The procedure, on admission to a hospital, that I recommend in cases of respiratory embarrassment due to "stove-in chest" is this:

1 Anæsthetise the patient straight away in order to achieve controlled respiration.

2 Examine the patient and assess the relative priorities of multiple injuries.

3 Eliminate the additional burdens of hæmothorax, pneumothorax, tamponade, dilatation of the stomach, or

diaphragmatic hernia, by appropriate catheterisation, sealed drainage, or suction.

4 Improve the efficiency and ease of respiration by tracheostomy if necessary

5 Institute controlled respiration using a mechanical breathing machine in desperate cases

6 Control pain by local injections of anæsthetic solution. Do not give morphine unless or until efficient respiration is assured.

If, after tracheostomy, it be decided that a mechanical breathing machine must be used, adequate apparatus and personnel must be available A patient kept alive artificially in this way requires constant medical and nursing care, at least in the early days of treatment.

The high mortality associated with " stove-in chest " is due to cardiorespiratory failure, and notably to anoxia and carbon-dioxide retention

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

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SUCCESSIVE advances in the treatment of high blood-pressures have been made possible by the steady output of new and improved drugs Until recently all the really potent drugs acted by blocking the autonomic ganglia Pressure reduction was invariably accompanied by partial paralysis of the parasympathetic system with consequent dry mouth, blurred vision, constipation, and impotence In some patients episodes of paralytic ileus threatened life, particularly when renal function was impaired Because of these difficulties only the most severely ill were selected for treatment The severity of side-effects varied greatly from patient to patient, but only a minority were unable to tolerate the regime All patients, however, had to endure inconvenience and even at times incapacity from the drugs and this made it difficult to achieve optimal pressure reduction in all The elimination of these parasympathetic side-effects would clearly be a desirable contribution by improving the toleration of treatment

The first lead towards a drug of this type was TM10 (Hey and Willey 1954), which had a selective paralytic action on the postganglionic adrenergic neurones but unfortunately also stimulated parasympathetic fibres—a property which made it useless therapeutically (Bain and Fielden 1957) Recently a much more promising drug, bretylium tosylate ('Darenthin'), has been described (Boura et al 1959) This drug paralyses adrenergic neurones without significant effect on the parasympathetic system These workers reported the results of treatment in 36 patients with hypertension, and in every patient except 1, who had a phæochromocytoma, pressure reduction was achieved In 4 patients the treatment had to be stopped because of symptoms associated with postural hypotension Side-effects were trivial, and the only one of importance was stuffiness of the nose In view of this encouraging report we have employed bretylium in the treatment of severe hypertension, at first only in those suffering severely from side-effects of ganglion blockade and later in a number of new patients receiving treatment for the first time The main difficulties encountered resulted from the variability of the degree of fall of blood-pressure, and studies of absorption were made to clarify this problem

Patients and Methods

A total of 50 patients were given oral maintenance treatment with bretylium during the six-month period of this trial 28 of them had previously been treated with ganglion-blocking drugs, usually pempidine or mecamylamine Initially only those patients with very severe side-effects or poor control of blood-pressure were transferred from the ganglion-blocking drugs, but later some with less severe side-effects were switched to bretylium All the patients had severe hypertension and 22 had hæmorrhages, exudates, or papillœdema in the retina when treatment had first been started. Other indications for treatment included hypertension with chronic renal disease, hypertension in pregnancy, hypertensive heart-failure, and severe high pressure and symptoms

All the patients were admitted to hospital for stabilisation on bretylium. 5 patients were first treated with intravenous doses of bretylium because acute reduction of the blood-pressure was required Intravenous treatment was unsatisfactory, and subsequently all patients were treated with the 200 mg oral tablets of bretylium tosylate The usual starting dose was 600 mg daily given as one tablet after breakfast, lunch, and supper The dose was increased daily by 300 to 600 mg until a satisfactory fall in the pressure was achieved In hospital the blood-pressure was recorded with the patient lying down and standing up at least four times daily Patients with malignant hypertension or left ventricular failure were nursed propped up on pillows and with the bed head raised on 12 in. blocks Less severely ill patients were encouraged to sit in chairs or walk about the ward as much as possible Outpatients were seen at short intervals in a special clinic for hypertensive patients

Absorption Studies

Bretylium labelled with ^{14}C was available as a sterile solution containing 5 μC of radioactivity with 30 mg of bretylium iodide for intravenous use and 5 μC with 200 mg bretylium tosylate for oral use The maximum dose approved for use in patients was 5 μC because of the long half life of ^{14}C As the permissible dose was small measurements had to be confined to the excretion in the urine after oral and intravenous doses The twenty-four-hour excretion after an oral dose was measured in 10 fasting patients 6 other patients were studied on two separate occasions to compare the eight-hour excretion. The twenty-four-hour excretion of bretylium after intravenous doses was measured in 6 patients, 4 with normal renal function and 2 with blood-urea values of about 120 mg per 100 ml

^{14}C was counted in a liquid scintillation counter (Jones et al in press) 1 ml urine samples were added to the toluene-alcohol-scintillator mixture and counted directly Errors from quenching due to other constituents of urine were avoided by counting the standards in the presence of equal quantities of the same urine samples

Results

ABSORPTION AND EXCRETION STUDIES

Intravenous Doses

The total excretion in twenty-four hours following an intravenous dose is tabulated in table I The recovery in

TABLE I—TWENTY-FOUR-HOUR EXCRETION AFTER INTRAVENOUS ^{14}C BRETYLIUM DOSES

Case no	Blood-urea (mg per 100 ml)	24-hr excretion (%)
1	37	65
2	40	60
3	36	83
4	32	74
5	115	23
6	120	31

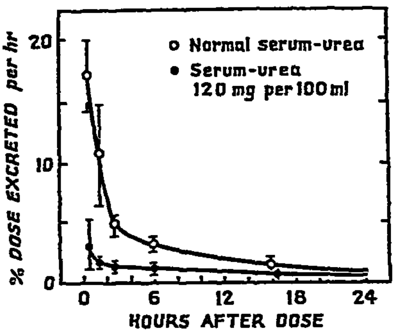

Fig 1

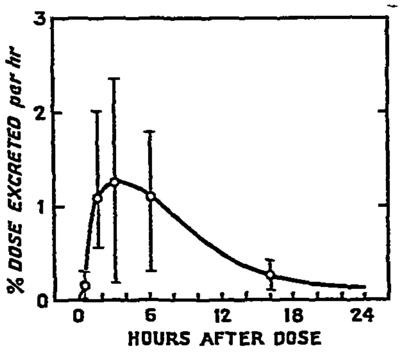

Fig 2

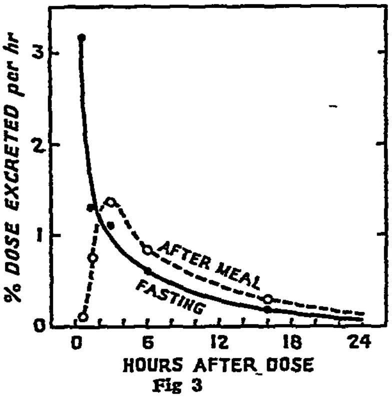

Fig 3

Fig 1—Fractional excretion of ^{14}C bretylium for 24 hours following intravenous administration in 4 hypertensive patients with a normal blood-urea and 2 with a blood-urea of about 120 mg per 100 ml. Open circles indicate mean excretion in patients with a normal blood-urea and closed circles the uræmic patients. The vertical lines show the range.

Fig. 2—Fractional excretion of ^{14}C bretylium in 7 patients given oral doses while fasting. The circles indicate the mean excretion per hour at the midpoint of each collection period, and the vertical lines show the range.

Fig 3—Fractional excretion of ^{14}C bretylium in a patient who showed a rapid initial excretion after a fasting dose and was given a second dose after a meal.

the 4 patients with normal blood-urea ranged from 65 to 83% with a mean of 71%. The 2 patients with a raised blood-urea excreted only 23% and 30%. The fractional excretions of these 2 patients are compared with those of the other 4 patients in fig 1.

Oral Doses

10 patients were given 5 μC oral doses of bretylium while fasting and the excretion was measured over the following twenty-four hours. The total excretion ranged from 5·1% to 18·3% with a mean of 12·9% (table II). The lowest excretion was from a patient with a blood-urea of 74 mg per 100 ml., another with a blood-urea of 79 mg per 100 ml. excreted 14·6% of the dose in twenty-four hours. The renal functions of the other patients may have been slightly impaired but the blood-urea concentrations were within the normal range. The fractional excretion was measured in 8 patients, and in 7 it showed a similar pattern (fig 2). Excretion was maximal between the second and eighth hours after the dose, but in 1 patient there was much more rapid initial excretion although the twenty-four-hour excretion was only 11·6%. This patient was restudied with the dose given after a meal, and the excretion then conformed to the more usual pattern (fig 3).

Paired absorption studies were made in 6 patients. The eight-hour excretion was compared when the dose was given fasting and again after a meal. Absorption was greater when the dose was taken fasting (table III).

These studies have proved the incomplete and probably irregular alimentary absorption that has a considerable bearing on the problems of treatment.

TABLE II—TWENTY-FOUR-HOUR URINARY EXCRETION AFTER ORAL ^{14}C BRETYLIUM DOSES

Case no	24-hr excretion (%)	Blood-urea (mg per 100 ml.)
7	17·9	44
8	6·7	34
9	11·6	30
10	18·2	44
11	14·5	79
12	5·1	74
13	10·4	30
14	17·0	32
15	12·8	39
16	15·2	40
—	Mean 12·9	—

TREATMENT OF HYPERTENSIVE PATIENTS

Intravenous Doses

4 patients with left ventricular failure and 1 with acute nephritis and hypertensive encephalopathy were treated with intravenous doses of bretylium iodide ranging from 200 to 600 mg. 1 patient with left ventricular failure had a satisfactory fall in blood-pressure, but the other 4 patients did not. All the patients were nauseated immediately after the injection and 4 of them vomited. This happened despite dilution of the dose 10:1 in 5% dextrose before injection.

TABLE III—EIGHT-HOUR URINARY EXCRETION AFTER ^{14}C BRETYLIUM ON TWO SEPARATE OCCASIONS

Case no	Dose after a meal (8-hr excretion) (%)	Fasting dose (8-hr excretion) (%)
17	6·9	9·1
18	13·4	21·4
19	12·9	18·5
20	0·1	8·4
21	9·6	16·0
22	4·1	6·7

Oral Maintenance Treatment

50 patients were started on oral maintenance treatment with bretylium tosylate. The final dose which controlled the pressure ranged from 200 mg to 3600 mg daily with a mean of 1800 mg. In 6 patients blood-pressure could not be controlled even with the largest doses. It is difficult to analyse concisely all the results obtained in this large group of patients. To facilitate presentation the patients have been divided broadly into those with a satisfactory result and those who were unsatisfactory.

Patients referred to as *satisfactory* had at least a 20 mm. Hg fall in the diastolic blood-pressure on standing or a standing pressure of 160/90 mm. Hg or lower.

Patients listed as *unsatisfactory* had either little reduction of blood-pressure or were intolerant of the drug in some way.

These data are shown in table IV with the hypertension divided into different groups. A striking feature is the poor results obtained in the patients with malignant hypertension, only 3 out of 11 were satisfactory. However, the patients without retinitis or papillœdema showed a much more favourable response, 21 out of 28 were satisfactory. The arbitrary division into satisfactory and unsatisfactory conceals all gradations from excellent to

TABLE IV—RESULTS OF TREATMENT WITH ORAL BRETYLIUM

Indication for treatment	Satisfactory	Unsatisfactory	Total
Malignant hypertension (papillœdema)	3	8	11
Grade-3 hypertension (retinal hæm or exudate)	6	5	11
Hypertension complicating chronic nephritis	7	2	9
Other severe hypertension with symptoms	11	3	14
Left ventricular failure	2	0	2
Hypertension in pregnancy	1	2	3
All causes	30	20	50

disastrous, but it does convey the overall picture without much distortion Many of the patients who had previously been treated with ganglion-blocking drugs were deeply grateful for the freedom from constipation, and for some the change was so dramatic that they were almost lyrical in their praise of bretylium A number of young hypertensives treated from the beginning with bretylium showed an excellent response and the drug seemed to interfere very little with their daily life

Causes of Treatment Failure

The high proportion of unsatisfactory responses in the malignant group makes it worth while to examine them in more detail The 3 responses regarded as satisfactory included the only 2 malignant hypertensives treated with bretylium from the beginning Both these patients have shown regression of hæmorrhages, exudates, and papillœdema with treatment The 3rd had rather less satisfactory control of blood-pressure, but he developed a subacute dissecting aneurysm of the aorta and died of uræmia There is no reason to incriminate this particular drug in this disaster The 8 patients with malignant hypertension whose response was unsatisfactory had all been treated previously with ganglion-blocking drugs and had proved difficult to manage 5 of them were not controlled by large doses of bretylium (2400–3600 mg daily) with added chlorothiazide and had to be transferred to other drugs, 2 of them subsequently died of uræmia and the other 3 are at present being treated with pempidine 2 of these patients initially responded to moderate doses of bretylium, and the 3rd, who was having 3600 mg of bretylium daily, had one severe fall of pressure although it remained very high on numerous other occasions Of the remaining 3 patients 1 is being treated with a combination of bretylium and pempidine and the other 2 are inadequately controlled by bretylium at present but have not reached maximum doses

Among the less severe hypertensive patients there were fewer failures, and most of these were caused by fluctuations in the pressure-lowering action 2 patients had minor strokes and 1 a myocardial infarction during periods of low pressure, fortunately all 3 recovered completely Abrupt falls of pressure are a serious hazard in patients with vascular disease of the brain or myocardium, and they seem to occur more commonly with bretylium than with the more regularly absorbed pempidine or mecamylamine Several patients who had been accustomed to ganglion-blocking drugs complained of a feeling of insecurity with bretylium because they could not predict when postural hypotension might occur For this reason 3 of them asked to return to ganglion-blocking drugs even though in other respects they preferred bretylium

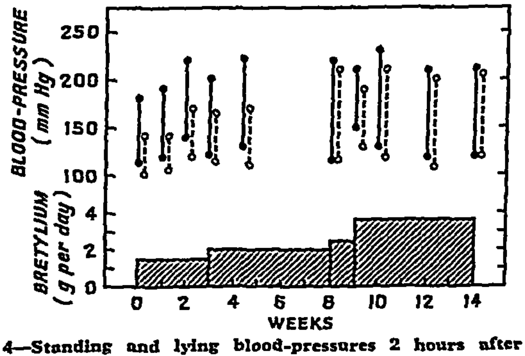

Fig 4—Standing and lying blood-pressures 2 hours after the morning bretylium dose at intervals over a period of 14 weeks in a patient with malignant hypertension

Tolerance

Minor degrees of tolerance may have passed unnoticed while the dose was slowly increased to gain control of the blood-pressure Over longer periods a number of patients required increasing doses to secure the same reduction of blood-pressure 1 such patient was well controlled with 1500 mg daily at the beginning, but over the succeeding three months required a progressive increase to 3600 mg daily (fig 4), when this dose proved ineffective the patient had to be transferred back to pempidine Fortunately most patients have required only moderate increases, but the margin between present dosage and the maximum daily intake of, say, 18 tablets is small

Side-effects

Many patients noticed mild nausea with oral bretylium, and 2 uræmic patients were troubled by both nausea and vomiting which ceased when the drug was stopped Nasal stuffiness was frequently present but only 2 patients volunteered complaints about it 2 patients complained of tightness of the skin around the nose and lower eyelids, and in 1 this was associated with severe nasal stuffiness 4 patients noticed tenderness of the parotid gland at the angle of the jaw, especially when eating 3 patients noticed visual impairment, in 2 of them objects close up seemed blurred, perhaps owing to accommodation difficulty, and the other noticed undue brightness of vision at a time when the pupil was small—for which we have no explanation 1 patient developed a fine papular erythematous rash which disappeared when bretylium was stopped When broken tablets had to be given some patients complained about the very bitter taste About two-thirds of the patients, however, were not subjectively troubled to any important extent

Deaths

5 patients who had been treated with bretylium died during the period of this study 2 died of uræmia, 1 of a dissecting aneurysm, 1 of cerebral hæmorrhage, and 1 of polyneuritis of the Guillain-Barré type

Discussion

Our experience with bretylium suggests some general conclusions about its place in the treatment of severe hypertension Bretylium is an effective drug which has a low incidence of serious side-effects It is probably the drug of first choice for "benign" hypertensive patients without ischæmic vascular disease who are being treated for the first time In patients with cerebral or myocardial ischæmia a fully-absorbed drug such as pempidine or mecamylamine is probably safer Any potent hypotensive drug may, rarely, precipitate a stroke or myocardial infarction in patients with occlusive vascular disease, but the risk is greater with a drug such as bretylium which gives rise to occasional unpredictable severe falls of blood-pressure. Some of the fluctuations in the hypotensive action of bretylium must be the result of variable absorption. This is to be expected with any drug which is poorly absorbed from the gut, because small changes in the proportion absorbed (say from 6 to 12%) may cause relatively large changes in the pharmacological effect. The results for the excretion of bretylium after oral and intravenous doses are comparable with the results obtained by Milne and Oleesky (1951) and Harington (1953) in studies with the quaternary-ammonium ganglion-blocking drug, hexamethonium. The only important difference is that the mean twenty-four-hour excretion of bretylium after oral doses is 12.9%, whereas for hexamethonium it is 5.4%. As the absorption of bretylium is appreciably greater than that of hexamethonium, fluctuations in absorption could be less dangerous. The patient who showed a very rapid initial absorption after a fasting oral dose of bretylium is of interest because this may account for sudden falls of pressure observed in some patients. The paired eight-hour excretion studies showed that the absorption after a fasting dose was always greater than after a meal. The slow excretion of bretylium after intravenous doses in patients with uræmia emphasises the need for care with these patients, who may accumulate the drug over several days and then become suddenly and persistently hypotensive. 1 such patient was faint on standing for five days after stopping oral bretylium.

Patients with severe hypertension, particularly malignant hypertension, required large doses of bretylium to control the blood-pressure. When bretylium proved ineffective in maximum doses the addition of chlorothiazide or strict sodium restriction caused a moderate increase in the hypotensive action. More than half (13 out of 22) of the severe hypertensives were not controlled by these measures and had to be transferred back to ganglion-blocking drugs. Some of these patients were at first controlled by bretylium but became unresponsive after weeks or months. Tolerance of this kind is a serious problem because the difference between the effective dose and the maximum dose is often small. There is a real need for a drug which retains the pharmacological specificity of bretylium but which has a greater activity per unit weight.

The overall results of treatment with bretylium in our series were less good than those recorded by Boura et al. (1959) and by Smirk and Hodge (1959). There are two possible explanations of this discrepancy. Our series contained a high proportion of very severe hypertensives and a number of patients who had responded poorly to large doses of ganglion-blocking drugs. These patients proved to be relatively insensitive to bretylium. The second possibility is that longer follow-up has revealed a larger number of patients in whom bretylium is becoming less effective.

In the present trial patients who had retinal hæmorrhages, exudates, or papillœdema fared badly when they were treated with bretylium. It is, therefore, inadvisable to switch such patients to bretylium if their blood-pressure is well controlled by other drugs. If patients with retinitis have side-effects which are so severe that pressure control has to be relaxed it may be useful to try them on bretylium. Patients without retinitis or papillœdema can be transferred without much difficulty, and less severe side-effects may make the change desirable.

Bretylium is a step forward along a difficult road. It allows control of blood-pressure in many patients without some of the miseries that accompanied ganglion blockade, but it is less reliable than pempidine or mecamylamine as a pressure-lowering agent. The reduction of blood-pressure is brought about by sympathetic paralysis and in consequence the management of the patient on bretylium is very similar to that of patients on ganglion-blocking drugs. Frequent follow-up and careful adjustment of the drug dose are essential if good results are to be sustained.

Summary and Conclusions

Bretylium tosylate facilitates the management of hypertensive patients on long-term oral treatment because of the low incidence of side-effects. The best results were obtained in hypertensive patients without retinal hæmorrhage, exudates, or papillœdema, and in this group 75% showed a satisfactory response. Only 41% of the patients with retinitis or papillœdema were satisfactorily managed. The malignant hypertensive patients who had been difficult to manage with pempidine or mecamylamine usually proved insensitive to oral bretylium in the doses used in this trial.

10 hypertensive patients given ^{14}C-labelled oral bretylium excreted a mean of 12.9% of the dose in twenty-four hours. 4 hypertensive patients given intravenous doses excreted a mean of 73% in twenty-four hours. Irregular and incomplete absorption after oral administration probably contributed to the variable falls of pressure in some patients. Such unpredictable falls of blood-pressure are dangerous in patients with occlusive vascular disease of the brain or heart.

We should like to thank Dr. David Long, of the Wellcome Foundation, for supplies of labelled bretylium.

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RENAL POLYCYTHÆMIA

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THE association of polycythæmia with renal carcinoma has now been reported in over 30 patients, and the subject has been reviewed by Damon et al. (1958) and Forssell (1958). The occurrence of polycythæmia with renal tumours other than carcinoma has been described in 2 cases (DeMarsh and Warmington 1955, Lawrence and Donald 1959). Where nephrectomy has been possible long remissions of the polycythæmia have occurred in some cases.

Recently there have been a few reports of polycythæmia with non-neoplastic renal lesions, polycystic kidneys were present in 4 of these cases (Forssell 1958) and hydronephrosis in 3 (Cooper and Tuttle 1957, Gardner and Freymann 1958, Lawrence and Donald 1959). This combination is probably commoner than the few reports of it would suggest; thus Kurrle (1954) described as a case of Gaisbock's syndrome a patient in whom polycythæmia and hypertension were associated with polycystic kidneys. In 5 of these 8 cases the diagnosis of polycythæmia was established by measuring the total red-blood-cell volume indirectly by plasma-volume/hæmatocrit methods. In 1 case it was shown that the red-cell volume diminished after nephrectomy.

We report here 2 cases of polycythæmia associated with non-neoplastic renal disease. In both patients polycythæmia disappeared after nephrectomy.

The relationship between renal disease and excessive erythropoiesis acquires added significance in the light of experimental work implicating the kidney as one possible source of erythropoietin (Jacobson et al. 1957, Osnes 1958). In the 2 cases reported here plasma-erythropoietin levels were initially elevated and fell to normal after nephrectomy.

Methods

Red-cell volume was measured by the ^{51}Cr method (modified from Veall and Vetter 1958).

Plasma volume was determined with an Evans-blue dye technique.

Lean body mass.—For reasons discussed later red-cell volume was related to lean body mass (L.B.M.). The latter was calculated from the total body-water (T.B.W.) using the relationship $\frac{\text{T.B.W.}}{0{\cdot}73} = \text{L.B.M.}$ (Pace and Rathbun 1945). The volume of distribution of administered urea was considered to measure T.B.W. (McCance and Widdowson 1951). Three estimations of the urea space were made on each occasion (Prunty et al. 1959).

Iron metabolism.—Plasma-iron levels were measured by the method of Bothwell and Mallett (1955). Plasma-^{59}Fe half-clearance times ($T^{1}/_{2}$) were determined by standard procedures (Veall and Vetter 1958). The disappearance-rate constant is given by $\frac{\text{Log}_e 2}{T^{1}/_{2}}$. From these data may be calculated the *plasma-iron turnover*, which was expressed as mg. per 100 ml. blood per day (Bothwell et al. 1957).

Plasma erythropoietin activity was assayed by a technique which is to be described elsewhere (Payne 1960). Briefly this is a "four-point" bioassay using the reticulocytosis induced in rats by intraperitoneal injections of graded doses of the subject's plasma. In each group of assays the test plasma is compared with pooled normal plasma. Considerable experience with this technique has now been obtained, and the reproducibility and validity of its results are established.

Case-reports

CASE 1.—A 57-year-old man was admitted to hospital in April, 1959, with left hemiplegia of sudden onset. During the previous two years he had experienced "bursting" feelings in the head, particularly on stooping. On examination the following findings were noted: left hemiplegia, blood-pressure 210/120 mm. Hg, normal optic fundi, auricular fibrillation, signs of mitral stenosis, no rise in jugular venous pressure, a large cystic mass palpable in the abdomen extending from the left loin to the suprapubic area.

The urine contained 60 mg. protein per 100 ml., a few leucocytes and red blood-cells, and was sterile. Electrocardiography confirmed auricular fibrillation, a chest X-ray showed a slightly enlarged heart shadow, blood-urea levels varied between 40 and 48 mg. per 100 ml., plasma sodium, potassium, chloride, and bicarbonate levels were within normal limits on several occasions, creatinine clearance was 85 ml. per minute, intravenous pyelography showed a normal calyceal pattern in the right kidney but no excretion of dye by the left kidney, and retrograde pyelography revealed a very large left hydronephrosis.

The patient appeared plethoric, and was found to have a hæmoglobin of 21·8 g. per 100 ml., a packed-cell volume (P.C.V.) of 62%, a red-blood-cell count of 6,800,000 per c.mm., a white-blood-cell count of 9,900 per c.mm. with a normal differential cell-count, a platelet-count of 171,000 per c.mm., and an erythrocyte-sedimentation rate of 1 mm. in the first hour (Westergren), the highest values recorded are quoted.

Examination of the sternal marrow showed slight erythroid hyperplasia. The spleen was not palpable. The total body-weight was 72·0 kg., the urea space 42·8 litres, and the lean body mass 58·6 kg.

The diagnosis of polycythæmia was established by the finding of an increased red-cell volume (R.C.V.). Further investigations of the polycythæmia are described under "Results". Despite the absence of cyanosis the presence of the heart lesion made it important to exclude an anoxic cause of the polycythæmia; the arterial blood-oxygen saturation was normal (95%).

On June 8, 1959, left nephrectomy was performed. A huge thin-walled hydronephrotic sac containing about 6 litres of milky fluid was found; this fluid was sterile. No kidney tissue could be identified macroscopically, and histological examination of the sac wall showed fibrous tissue infiltrated by chronic inflammatory cells and containing a few renal tubular elements. At operation blood samples were obtained from the aorta, the left renal vein, and a peripheral arm vein at the same time. These samples were assayed for erythropoietin activity, and the results are discussed later.

Postoperatively the patient's recovery was uneventful. Subsequent changes in hæmoglobin and hæmatocrit levels are shown in fig. 1. The white-cell and platelet counts remained normal. Postoperative studies of red-cell volume, iron metabolism, and erythropoietin levels are described below.

CASE 2.—This obese 55-year-old railwayman was found to have auricular fibrillation at a routine medical examination. When he was admitted to hospital no other signs of heart-disease were found; there was no evidence of cardiac failure, the blood-pressure averaged 160/90 mm. Hg, the heart was not enlarged radiographically, and electrocardiography showed only auricular fibrillation. He appeared to be euthyroid. An unsuccessful attempt was made to bring about reversion to normal cardiac rhythm with quinidine.

The patient had a plethoric complexion and was found to have a hæmoglobin of 18·8 g. per 100 ml., P.C.V. 57%, a platelet count of 185,000 per c.mm., a white-blood-cell count of 13,000 per c.mm. (neutrophils 80%, lymphocytes 16%, monocytes 4%), the highest values recorded are quoted. The spleen was not palpable. The diagnosis of polycythæmia was confirmed by the finding of an increased red-cell volume. Further studies of the polycythæmia are described below.

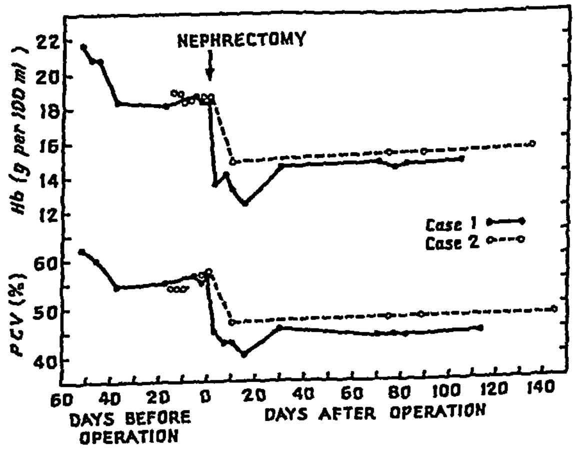

Fig. 1—Hæmoglobin and hæmatocrit values before and after operation.

TABLE I—RED-CELL VOLUME AND ^{59}Fe RESULTS BEFORE AND AFTER OPERATION

Case no	Time	Red-cell volume		Plasma volume (ml. per kg)	Plasma-iron (µg per 100 ml)	$T^1/_2$ ^{59}Fe (min)	^{59}Fe-disappearance-rate constant (hr $^{-1}$)	Plasma-iron turnover (mg per 100 ml blood per day)
		(ml)	(ml per kg body-weight)					
1	2 weeks preop	2805	39·0	45 6	91	54	0 77	0 80
	4 weeks postop	2103	32 2	49 5				
	11 weeks postop	2165	30 5	48 8	102	75	0 55	0 75
2	2 weeks preop	3317	33 2	32 8	75	28	1 49	1 20
	11 weeks postop	2468	25 7	35 6	88	72	0 58	0 64
Normal values					70–180	70–140	0 33–0 69*	0 38–0 77†

* Bothwell et al (1956) † Bothwell et al (1957)

The total body-weight was 100 kg , the urea space 52 0 litres, and the lean body mass 71 3 kg

To exclude a renal cause of the polycythæmia intravenous pyelography was performed. The left kidney appeared normal, but on the right side the upper calyceal group was much dilated, the upper pole of the kidney was enlarged, and a rounded indentation of the calyx was seen. The blood-urea was 25 mg per 100 ml and the creatinine clearance was 75 ml. per minute The urine contained an occasional leucocyte but no protein and was repeatedly sterile, no tubercle bacilli were seen in it, and Löwenstein cultures were negative The right kidney was explored surgically on May 2, 1959, and a large multilocular cyst was removed from the upper pole Several smaller cysts were present in the remainder of the kidney, but this was left in situ as considerable normal tissue appeared to be present Histological examination of the cyst showed the wall to be largely fibrous although lined in part by cuboidal epithelium. There was no evidence of malignant change.

Postoperatively the patient has remained well for six months to date, although auricular fibrillation has persisted Three months after operation the following findings were obtained Hb 15 1 g per 100 ml , P.C.V 48%, platelets 270,000 per c.mm , white blood-cells 8900 per c.mm. The R.C.V was now normal Further studies are described below

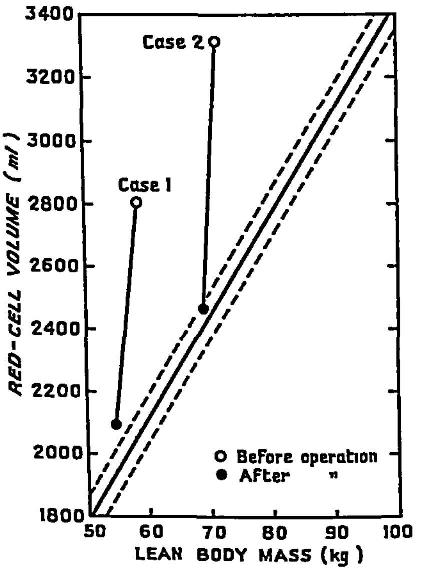

Fig 2—Red-cell volumes before and after operation

The solid regression line relating the normal mean red-cell volume to lean body mass is taken from the data of Muldowney (1957), ($y = 32\ 74\,x + 155\ 17$) The interrupted lines represent 95% confidence limits

Results

Red-cell Volume, Hæmoglobin, and Hæmatocrit (see table I and figs 1 and 2)

Before nephrectomy both patients had raised hæmoglobin concentrations 21 8 g and 18 8 g per 100 ml The highest hæmatocrit values were 62% in case 1 and 57% in case 2 After operation the hæmoglobin and hæmatocrit values returned to normal (fig 1) and have remained so

In case 1 the red-cell volume (R C V) before operation was found to be 2805 ml , whereas the upper 95% confidence limit for normal R C V predicted from the lean body mass was 2145 ml Four weeks after nephrectomy the R C V was 2103 ml Owing to weight loss the predicted upper limit of normal at this time was 2014 ml

In case 2 the R C V before nephrectomy was 3317 ml , whereas the upper limit of normal R C V was 2564 ml Eleven weeks after operation the R C V was 2468 ml

Plasma-iron Turnover (see table I)

In each case before operation the plasma-^{59}Fe half-clearance time was shortened (54 minutes and 28 minutes) while the turnover of iron through the plasma was increased (0 80 and 1 20 mg per 100 ml blood per day) Eleven weeks after nephrectomy the plasma-^{59}Fe half-clearance times had returned to normal (75 and 72 minutes) and so had the plasma-iron turnover (0 75 and 0 64 mg per 100 ml blood per day) The change in plasma-iron turnover was much greater in case 2 than in case 1

Erythropoietin (see table II)

Before nephrectomy the plasma-erythropoietin activity was raised to 8 times normal in case 1 and 43 times normal in case 2 The erythropoietin levels eventually became normal after removal of the diseased kidney

In case 1 blood samples were obtained at operation from the left renal vein (the side of the hydronephrosis), from a peripheral arm vein, and the aorta The peripheral venous erythropoietin level was elevated to the same degree as in the preoperative specimens (8 times normal) The aortic and left renal venous samples, however, contained much less erythropoietin activity (twice normal)

Discussion

The essential feature of polycythæmia is an increased total red-cell volume, and Lawrence (1955) has stressed the danger of diagnosing polycythæmia on hæmoglobin concentration, hæmatocrit, or red-cell counts when these are not grossly abnormal Even when the red-cell volume is known the significance of borderline values may be difficult to decide since the normal red-cell volume of a given subject cannot be predicted from his weight with any accuracy Muldowney (1957) has shown that the

TABLE II—ERYTHROPOIETIN ASSAYS BEFORE AND AFTER OPERATION

Case no	Time	Site of blood sample	Erythropoietin level (times normal)*
1	2 weeks preop	Antecubital vein	8
	At op	,, ,,	8
		Lt renal vein	2
		Aorta	2
	4 weeks postop	Antecubital vein	3
	16 weeks postop	,, ,,	1
2	2 weeks preop	,, ,,	43
	11 weeks postop	,, ,,	8
	19 weeks postop	,, ,,	1

* 95% confidence limits 60–160% this implies that 95 times in 100 the true mean would lie within these limits

fat-free body mass (lean body mass) is a much more accurate parameter for red-cell volume, and we have confirmed this relationship (Hyde and Jones 1960) The red-cell volumes in our 2 subjects were therefore related to lean body mass (see fig 2) The results show that in each case there was initially a true increase in the circulating red-cell volume Eleven weeks after nephrectomy case 2 had a normal red-cell volume Four weeks after nephrectomy case 1 had a red-cell volume which was only 90 ml above the upper limit of normal, compared with a preoperative value which exceeded this limit by 760 ml At this time the plasma-erythropoietin level had not yet returned completely to normal The operation was virtually bloodless in each case, and no other specific therapy was given

In each case reported here the plasma-iron turnover was initially increased but became normal after nephrectomy This change reflects the postoperative fall in red-cell production that may be inferred from the return to normal of the red-cell volume, hæmoglobin concentration, hæmatocrit, and plasma-erythropoietin level

Gardner and Freymann (1958) concluded from a survey of published reports that the percentage of plasma-iron removed per hour (i e , the ^{59}Fe-disappearance-rate constant × 100) was significantly greater in polycythæmia vera (209 7%±96 9%) than in secondary (anoxæmic) polycythæmia (79 5%±29 6%) In the case of polycythæmia with hydronephrosis reported by these workers the percentage of plasma-iron removed per hour was 210, thus resembling polycythæmia vera in this respect In the 2 cases we report the corresponding figures were 77% and 149%, the first being within the range cited for secondary polycythæmia while the second resembles more closely that for polycythæmia vera It does not seem likely that this parameter will prove a useful one with which to contrast primary and renal polycythæmia

The existence of one or more humoral factors (erythropoietin) controlling erythropoiesis is now widely recognised, and it has been shown that plasma-erythropoietin levels are raised in polycythæmia vera (Contopoulos et al 1957, Linman and Bethell 1957) An increasing body of experimental work suggests a close relationship between the kidney and plasma-erythropoietin (Jacobson et al 1957, Goldwasser et al 1958, Naets 1958, Osnes 1958, Lange et al 1959) The plasma-erythropoietin level is not raised in the anæmia of chronic renal failure (Lange et al 1959), whereas erythropoietin levels are elevated in most other anæmias (Piliero et al 1956, Gordon 1959) This difference has been taken as evidence that the anæmia of chronic renal failure results from inadequate production of erythropoietin by the damaged kidneys

Previous studies of renal polycythæmia have not included measurements of erythropoietin In the present 2 cases the elevated erythropoietin levels and the subsequent fall to normal after nephrectomy further support the concept of an intimate relationship between plasma-erythropoietin and the kidney

Much of the above work suggests that in certain pathological conditions the kidneys may produce increased amounts of erythropoietin However, Hirsjärvi (1955, 1958) has reported experiments indicating a peripheral activation, or formation, of erythropoietin The finding in case 1 that the venous blood draining from the hydronephrotic kidney had a lower erythropoietin level than blood from an arm vein is further evidence of such a peripheral mechanism How some kidney lesions might affect this remains uncertain and further work is needed to clarify the relationship between the kidney and erythropoietin

The association of polycythæmia with renal carcinoma has been reported in at least 34 cases (see Damon et al 1958 and Forssell 1958) In a series of 205 patients with polycythæmia, Damon et al (1958) found 9 cases of renal carcinoma (an incidence of 4 4%) Lawrence and Donald (1959) found that renal carcinoma occurred in 0 93% of a series of 325 polycythæmic patients, whereas the expected incidence of renal carcinoma in America is 0 003% These figures suggest that this association is not fortuitous The long remissons of the polycythæmia that have followed successful nephrectomy is further evidence for this conclusion

Coexistent polycythæmia and non-neoplastic renal disease have been reported to date in 10 cases (see table III) The numbers of any one type of renal lesion are as yet too small to exclude a chance association, and the true prevalence of kidney disease associated with polycythæmia remains unknown Increasing awareness of this syndrome may well lead to more frequent recognition It is interesting that in 3 of the 6 cases with polycystic kidneys this condition was unilateral

In addition to the 2 cases reported here the results of nephrectomy in polycythæmia associated with non-neoplastic renal lesions are available in 4 other patients, and in each case remission of the polycythæmia has occurred In 3 of these cases (including both our patients) no other specific therapy was given These facts are further evidence of a causal relationship between certain renal lesions and polycythæmia

TABLE III—DETAILS OF REPORTED CASES WITH POLYCYTHÆMIA AND NON-NEOPLASTIC RENAL DISEASE

Source	Renal disease	Age (yr)	Sex	Hb (g per 100 ml)	P C V (%)	Red cells (× 10⁶)	Red cell volume (ml per kg)	Blood-volume	White cells (per c mm)	Platelets (per c mm)	Palpable spleen	Blood-pressure (mm Hg)	Nephrectomy	Remission after nephrectomy‡	Other therapy
Cooper and Tuttle (1957)	Hydronephrosis	55	M	19 0	68			7750 ml	11,300	360,000	No	150/100	Yes	6 yr	V•
Gardner and Freymann (1958)	,,	65	M	21 4	68	6 88	10 9	70 2 ml per kg	11,050	Normal	No	190/120	Yes	2 yr	V•
Lawrence and Donald (1959)	,,	37	M	23 0		9 60			10,700	750,000	No	110/95	Yes	18 mos	V• ^{32}P
Present case 1	,,	57	M	21 8	62	6 80	39 0	81 5 ml per kg	9,900	171,000	No	210/120	Yes	6 mos	
Present case 2	Polycystic rt kidney	55	M	18 8	57	6 60	33 2	66 0 ml per kg	13,100	185,000	No	160/90	Yes	7 mos	
Kurrle (1951)	Polycystic kidneys	12	M	144%		9 0			10 400	152,000	No	200/130	No		V• ^{32}P
Forssell (1958)	Polycystic rt kidney	61	M	126%†		6 28			7,200	136,000	No	Elevated	Yes	2½ mos	
,, ,,	Polycystic kidneys	32	M	111%†	74	8 10		9329 ml	Normal	Normal	Yes	Elevated	No		
,, ,,	Polycystic rt kidney	61	F	139%†	70	7 21		7190 ml	12,000	100,000	No	Elevated	No		
,, ,,	Polycystic kidneys	57	M	141%†	71	7 12		8267 ml	Normal	Normal	No	Elevated	No		

• Venesection † Sahli ‡ To date of publication

In polycythæmia vera increased white-cell and platelet counts are common, while the spleen is usually palpable at some stage of the disease Damon et al (1958) concluded that most patients with polycythæmia and renal carcinoma lack splenomegaly, leucocytosis, and thrombocytosis, so that the " polycythæmia " is more properly termed " erythrocytosis " The data in table III suggest that in polycythæmia associated with non-neoplastic renal lesions the spleen is usually impalpable and the platelet count usually normal White-cell counts greater than 10,000 per c mm were obtained in 6 of the 10 cases, but the figures cited are the highest obtained in each case and all may be within normal limits The results of bone-marrow examination are available in 7 of the 10 cases, and, whereas increased erythropoiesis was noted in 5 cases, no mention is made of excessive myeloid activity The available data are insufficient to decide whether hypertension is more common in renal polycythæmia than in polycythæmia vera In summary, renal polycythæmia is usually characterised by an erythrocytosis with normal platelet and white-cell counts while the spleen is impalpable

Certain practical implications follow from the recognition of this syndrome of renal polycythæmia The possibility of an underlying renal lesion should be considered in any polycythæmic patient, especially when white-cell and platelet counts are normal, and the spleen cannot be felt Examination of the urine, palpation of the loins, and intravenous pyelography should be undertaken in such a case Hæmaturia has sometimes been attributed to an abnormal bleeding tendency in polycythæmia Hæmaturia occurred, however, in most of the reported cases of polycythæmia with renal disease, and its occurrence should intensify the search for a renal lesion Because the polycythæmia may remit after nephrectomy, diagnosis of the kidney disease in renal polycythæmia is especially important

Summary

In 2 cases of polycythæmia—1 associated with hydronephrosis and the other with a unilateral polycystic kidney—the polycythæmia disappeared after removal of the renal lesions

Plasma-erythropoietin levels were raised before operation but fell to normal after nephrectomy

Plasma-iron turnover was initially increased but returned to normal after nephrectomy

The features of this type of polycythæmia and the part played by the kidney in the control of erythropoiesis are discussed

The syndrome of renal polycythæmia is probably commoner than is realised Diagnosis of the renal lesion is important because its removal may lead to remission of the polycythæmia

We wish to thank Dr G Wetherley-Mein and Dr Brian Creamer for much useful advice, Prof F T G Prunty and Dr J L Pinniger, for encouragement and permission to investigate these patients in the William Dunn and Louis Jenner Laboratories, and Dr R Daley and Dr Evan Jones, who allowed us to study and to report their patients

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EFFECT ON THE KIDNEY OF DRUGS CONTAINING PHENACETIN

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As early as 1950, Spuler and Zollinger in Switzerland drew attention to a chronic interstitial nephritis which they suggested was due to prolonged abuse of phenacetin-containing analgesics, since a very great proportion of their patients had been addicted to these preparations (Spuler and Zollinger 1953)

In attempts to reproduce the syndrome by animal experiments and to determine the significance of phenacetin, Studer and Zbinden (1955) demonstrated slight degeneration of the tubules but no genuine interstitial nephritis in rats given large doses of 'Saridone' for long periods On the other hand, Thölen et al (1956) were able to produce interstitial nephritis in corresponding experiments in mice, possibly because in these animals spontaneous urinary infection with *Clossiela muris* is common Moreover, Miescher et al (1958) produced interstitial nephritis in rabbits by feeding them with phenacetin and simultaneously giving *Escherichia coli* intravenously (injection of *Esch coli* in a control group did not produce renal injury)

Direct provocation experiments are probably necessary to demonstrate the relation of phenacetin to chronic interstitial nephritis in man In a series of patients who had abused phenacetin and whose renal function was reduced, we therefore undertook direct provocation experiments with pure phenacetin and with phenacetin contaminated with acetic-4-chloranilide (preparations of phenacetin usually contain this contaminant) Quantitative changes in the urinary sediment were used as a measure of renal irritation

Effects of Provocation

11 patients were given phenacetin entirely free from acetic-4-chloranilide, 8 patients had phenacetin containing 0 13% acetic-4-chloranilide, and 8 phenacetin containing 0 30% acetic-4-chloranilide For three days, all drugs were withdrawn and then the patients received 3 g daily of the phenacetin preparation for five days Both in the preliminary period and the five days of the experiment, sediment counting by

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TABLE I—ERYTHROCYTE COUNT IN TWELVE-HOUR URINE

Patient	Red cells (millions)							
	Control period			During treatment with 3 g pure phenacetin per day				
	1st day	2nd day	3rd day	1st day	2nd day	3rd day	4th day	5th day
1		3 7	7 3	9 1	2 3	7 7	1 0	
2	7 4	3 9	1 2	2 6	3 7	2 9	1 2	1 0
3	9 2	0 5	1 1	4 5	3 0	2 4	0 6	0 4
4	1 7	0 9	0 9	0 9	1 3	2 4	3 0	4 2
5	5 6	7 0	5 4	4 5	20 1	6 0	2 6	3 2
6	1·0	0 2	0 4	0 3	0 3	0 4	0 1	0 3
7	3 4	2 3	13 9	11 6	3 1	5 9	3 1	
8	0 8	0 6	0 6	1 0	1 8	1 7	1 5	
9	0 7	1 2	3 7	2 6	1 8	2 1	0 7	
10	0 5	0 8	0 9	0 5	0 9	0 8	0 4	0 6
11	0 1	0 0	0 4	0 5	0 6	0 3	0 5	1 1
				During treatment with 3 g phenacetin per day containing 0 13% acetic-4 chloranilide				
12	1 5	2 5	1 7	0 7	2 3	1 8	1 1	2 1
13	0 9	0 6	1 2	14 5	1 9	1 6	2 2	1·1
14	0 2	1 2	0 3	1 2	1 3	1 4	1 7	1 0
15	0 6	0 5	0 5	1 2	0 5	1 2	0 8	
16	0 1	0 0	0 2	0 4	0 2	0 7	0 4	0 3
17	9 4	3 7	4 2	5 7	3 5	4 6	2 0	3 0
18	0 4	0 4	0 5	0 1	0 1	0·2	0 6	0 5
19	0 2	0 1	0 3	0 1	0 6	0 8	0 8	0 6
				During treatment with 3 g phenacetin per day containing 0 30% acetic-4 chloranilide				
20	0 0	0 1	0 1	0 0	0 0	0 3	0 2	
21	0 2	0 1	0 2	0 2	0 3	0 8	0 4	1 0
22	1 0	0 8	1 2	1 8	1 1	2 2	1 1	1 5
23	0 3	0 1	0 2	0 4	0 1	0 2	0 2	0 2
24	0 1	0 1	0 2	0 2	0 2	0 2	0 2	0 2
25	0 1	0 1	0 0	0 3	0 1	0 2	0 1	0 1
26	0 5	0 1	0 3	1 0	0 2	0 6	0 3	0 3
27	1 8	1 3	5 3	2 6	5 3	6 2	1 1	7 1

TABLE II—LEUCOCYTE-COUNT IN TWELVE-HOUR URINE

Patient	White cells (millions)							
	Control period			During treatment with 3 g pure phenacetin per day				
	1st day	2nd day	3rd day	1st day	2nd day	3rd day	4th day	5th day
1		203 9	325 6	1051 8	383 6	354 2	216 7	
2	7 7	7 0	9 7	11 6	23 3	15 3	12 7	15 4
3	352 1	493 9	456 1	567 4	899 6	288 1	422 3	501 0
4	30 2	26 8	39 9	11 2	37 0	15 2	34 9	43 3
5	259 2	281 4	212 2	291 7	321 0	291 0	314 1	330 9
6	8 9	3 0	6 9	2 0	5 1	5 0	2 1	3 9
7	766 7	846 3	1179 7	900 9	693 5	660 1	241 0	
8	22 3	17 6	22 5	23 9	32 2	18 9	52 6	
9	69 2	61 9	170 6	103 4	50 9	82 2	45 5	
10	6 5	9 8	13 0	6 4	17 0	9 3	6 0	
11	0 6	0 3	0 1	0 4	1 6	0 4	1 1	2 2
				During treatment with 3 g phenacetin per day containing 0 13% acetic 4 chloranilide				
12	1383 5	1423 9	814 1	538 0	455 2	752 3	426 1	525 7
13	21 2	16 4	7 4	42 6	11 1	15 7	24 8	12 6
14	0 4	0 5	0 6	0 6	1 3	0 1	0 9	0 5
15	3 1	4 4	4 6	12 0	12 4	17 3	8 8	
16	1 7	4 2	5 6	6 5	4 0	7 6	12 3	19 9
17	31 3	10 6	43 0	108 9	48 8	86 2	27 2	70 9
18	26 5	11 1	26 4	16 8	13 6	18 7	41 4	20 6
19	1 3	1 1	5 3	5 4	7 5	14 1	4 0	5 3
				During treatment with 3 g phenacetin per day containing 0 30% acetic 4 chloranilide				
20	1 0	11 0	6 2	2 9	1 8	0 4	4 2	
21	55 3	76 3	75 7	84 3	73 3	54 7	299 8	286 7
22	209 9	169 1	151 0	151 7	161 3	171 2	217 4	163 8
23	18 0	5 4	5 6	1 7	4 2	7 7	1 5	3 6
24	1 5	3 7	4 0	1 6	1 8	7 4	5 0	10 2
25	0 7	0 6	0 1	0 5	1 0	1 1	1 4	0 5
26	72 6	101 9	122 2	76 1	111 3	95 5	411 5	68 9
27	171 7	194 6	123 6	103 4	315 8	214 5	149 5	320 8

the Addis method was undertaken daily on a twelve-hour sample of night urine to which toluol was added as preservative. The urinary sediments were counted immediately after collection of urine, and all counts were undertaken by one laboratory worker, experienced in the technique. In the analysis, only the erythrocyte and leucocyte values were considered.

The erythrocyte and leucocyte counts recorded are shown in tables I and II.

Probably because of the inexactitude of the counting method, the scatter of the twenty-four-hour values is great, so that the considerable variations from day to day make it hard to see directly whether the sediment values are higher than usual during provocation with phenacetin in individual patients. It proved suitable in the statistical analysis to use logarithmic values for the urinary sediments since the standard deviation of the logarithms, by and large, seemed to be independent of the absolute quantity of the urinary sediment in the individual patients. For each of the preparations of phenacetin the average logarithm of the sediment values in the preliminary period was compared with the corresponding value in the treatment period. The results of the statistical analysis were shown in table III.

A significant increase in the erythrocyte-count in the urinary sediment was found during treatment with both of the preparations containing acetic-4-chloranilide; on the other hand, a significant increase in the leucocyte-count was recorded only in the experiment in which phenacetin with 0 13% acetic-4-chloranilide was used. With pure phenacetin the increase in the erythrocyte-count was approximately 15% and in the leucocyte-count approximately 11%, but these differences were not significant.

Discussion

The results support the view that phenacetin-containing preparations may damage the kidney. Preparations containing acetic-4-chloranilide may be chiefly responsible, since the quantitative change in the urinary sediment is much more pronounced with them than with purified phenacetin. The observation that the effect of the most markedly contaminated preparation was less than that of a purer preparation may be explained by the fact that the patients in the last series had better renal function than those in the first two series. The degree of renal irritation may partly depend on the patients' renal function, being greatest when function is poor.

As Hald (1950) showed, the preparations of phenacetin at present available contain varying quantities of acetic-4-chloranilide as a contaminant. Analysis of 22 preparations of phenacetin revealed contamination varying from 0 02 to 0 64%. The *Danish Pharmacopœia*, which, with the exception of the *British Pharmacopœia*, is the only one to give directions on this subject, permits a maximum of 0 35% acetic-4-chloranilide. Acetic-4-chloranilide is a much more potent former of methæmoglobin than phenacetin (Gad et al. 1950), and the question arises whether abnormal hæmoglobin products may be responsible for the renal damage.

Phenacetin was originally manufactured by synthesis from 4-nitrophenol, and contamination with acetic-4-chloranilide did not occur. For twenty or twenty-four

TABLE III—COMPARISON BETWEEN URINE COUNTS BEFORE AND DURING TREATMENT WITH PHENACETIN

—	Mean of logarithms of absolute urine counts		Difference	t value
	Control period	During treatment		
Erythrocytes				
Pure phenacetin	0 139	0 201	0 062	0 97
Phenacetin with 0 13% acetic 4 chloranilide	−0 204	0 009	0 213	2 84*
Phenacetin with 0 30% acetic 4 chloranilide	−0 611	0 411	0 200	2 67*
Leucocytes				
Pure phenacetin	1 585	1 631	0 046	1·02
Phenacetin with 0 13% acetic 4 chloranilide	1 051	1 202	0 151	2 85*
Phenacetin with 0 30% acetic 4 chloranilide	1 249	1 248	− 0 001	− 0 02

*0 01 > P > 0 001

years, however, phenacetin has been prepared from 4-nitrochlorbenzol, with acetic-4-chloranilide as a by-product This change may explain why the toxic action of phenacetin-containing preparations was detected only in recent years

Summary

In recent years suspicion has arisen that chronic abuse of phenacetin and phenacetin-containing analgesics may cause severe renal damage The nephrotoxic effect of phenacetin was estimated in 27 addicts by quantitative determination of the urinary sediment by the Addis method

In 11 patients given purified phenacetin, a slight but not significant rise was registered, in 16 patients given phenacetin contaminated with acetic-4-chloranilide (a contaminant found in varying amounts in practically all preparations of phenacetin) the effect was much more pronounced, with significant rise in both erythrocyte and leucocyte counts As acetic-4-chloranilide is a much stronger former of methæmoglobin than phenacetin, renal damage may be caused by the abnormal hæmoglobins, and not by a direct toxic effect of phenacetin or related drugs

We wish to express our gratitude to Dr Jens Hald, of Meco-Dumex Ltd (former Medicinalco Ltd), for the interest taken in our work and for the suggestion that we examine the effect of acetic-4-chloranilide-containing drugs We also wish to thank Miss Inger Ladegård for technical assistance The work was supported by a grant from King Christian X's Fund

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SPEED OF ACTION OF ASPIRIN, SOLUBLE ASPIRIN, AND BUFFERED ASPIRIN

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ASPIRIN (acetylsalicylic acid) is probably the most widely prescribed drug in this country In 1954 3000 million tablets of aspirin were produced in the United Kingdom Recently various proprietary brands of acetylsalicylic acid have been recommended as having a faster action or fewer side-effects, but there seems to be no conclusive evidence in favour of these claims

Aspirin is absorbed from the stomach of dogs with the pylorus ligated, but it is absorbed most quickly from the intestine (P K. Smith 1949) Any factor which influences gastric emptying may therefore be expected to influence aspirin absorption correspondingly Bradley et al (1936) showed that aspirin itself caused an increase in gastric secretion and delay in gastric emptying, but whether it acts locally or by way of a central stimulus of gastric secretion is unknown (*British Medical Journal* 1952)

M J H Smith (1951) gave 6 subjects aspirin *B P* and a proprietary aspirin, and found higher serum levels with the proprietary preparation Paul et al (1950) similarly compared a buffered aspirin with aspirin *U S.P* and concluded that the buffered aspirin gave serum levels twice as high at 10 and 20 minutes after administration, but in their trial the two drugs were not compared in the same subjects More recently Cronk (1958) and Batterman (1958) compared buffered aspirin with a rapidly disintegrating non-buffered aspirin and found no significant differences after gr 10 doses in cross-over trials involving 9 and 20 subjects No mention is made of the method of administration of the tablets except that they were given by mouth

The present study concerns the speed of absorption of aspirin in normal subjects free from gastrointestinal disease, under strictly controlled conditions Each subject was given aspirin *B P*, soluble aspirin *B.P* (calcium aspirin), and two proprietary preparations—namely, acetylsalicylic acid plus aluminium carbonate and magnesium carbonate in small amounts ('Bufferin'), and acetylsalicylic acid plus glycine ('Paynocil')

Methods and Materials

There are several established methods for the estimation of plasma salicylate, the best-known being that of Brodie et al (1944) These, however, were developed mainly for measuring the high values occurring during the treatment of acute rheumatism, and were not easily applicable to the low serum levels of this trial Also, they involved the use of the toxic substance ethylene dichloride M J H Smith (1951) described a method for this type of study and this has proved satisfactory in my hands It was used unmodified except that the instrument used was a Cambridge 'Unicam' S P 600 with the red cell transmitting at 750 μ For serum levels below 10 mg per 100 ml the variation due to the method was less than 0 5 mg per 100 ml

Six healthy volunteers (aged 20–33) who had not taken any salicylate in the previous 72 hours were given gr 10 doses of aspirin in the four forms, using a double-blind technique The tablets, aspirin *B P*, calcium aspirin *B P*, paynocil, and bufferin were obtained and prepared by the hospital pharmacist and labelled A, B, C, and D, their identity was not revealed to the investigator until the statistical analysis had been made The tablets were given in predetermined random order using the method of roman squares—i e, the six subjects received the tablets A, B, C, and D in a different order This ensured that a given tablet was not always administered first or last and that on any particular day the tablets were being estimated side by side, eliminating as far as possible any bias due to variation in experimental conditions

The tablets were given under standard conditions 2 hours after the subject's normal breakfast. As stated previously, earlier trials have given little information on the method of administering tablets If swallowed whole, a tablet which is slow to disintegrate is likely to be at a disadvantage compared with one which disintegrates rapidly To avoid this discrepancy the tablets were crushed in 2 oz of water and the glass was then rinsed twice in 2 oz. of water so that the dose was taken in a total of 6 oz. of water The tablets differed considerably in the ease with which they were dispersed.

Blood was drawn by repeated venepuncture at 0, 10, 20, and 30 minutes, the time recorded being the moment of venous occlusion Each time 15 ml. of blood was withdrawn smoothly by dry syringe into a heparinised bottle containing added fluoride A pilot survey had shown that heparin caused no hæmolysis When oxalate or citrate was used hæmolysis was only slight, but it proved troublesome because it led to high "blank" values in the zero-time specimens

The collected specimens were then centrifuged and the serum-salicylate values estimated as mg sodium salicylate per 100 ml , almost exactly convertible into mg acetylsalicylic acid (molecular weight sodium salicylate=173, acetylsalicylic acid=180)

TABLE I—MEAN TOTAL SALICYLATE LEVELS (EXPRESSED AS MG SODIUM SALICYLATE PER 100 ML)

—	A Bufferin	B Soluble aspirin *B P*	C Paynocil	D Aspirin *B P*
10 minutes	2 3±1 02 (0 9–3 8) 6	3 2±1 9 (0 4–4 9) 6	2 4±1 12 (0 7–3 6) 6	1 3±0 57 (0 2–1 8) 6
20 minutes	4 8±1 01 (2 3–6 2) 6	5 4±2 01 (1 9–6 9) 6	4 0±1 57 (2 2–5 9) 6	2 7±1 08 (0 7–3·9) 6
30 minutes	5 4±1 03 (4 5–6 8) 4	5 3±1 35 (2 8–6 6) 6	4 6±1 57 (2 8–6 8) 6	3 3±1 09 (1 5–4 5) 6

Range in parentheses Number of observations below

Normal serum containing no salicylate gives a faint blue colour as compared with the reagent blank and this reading at zero time (varying with each patient but usually equivalent to about 0 5 mg acetylsalicylic acid, or less, per ml) was deducted from the readings obtained at the specified times to obtain the true salicylate levels at those times

Calibration curves were done repeatedly during the period of the trial and did not appear to differ significantly However, with each test a freshly prepared standard solution of 5 mg aspirin per 100 ml was run through in addition to the plasma and reagent blanks Occasional values are missing—e g , because of failed venepuncture, insufficient plasma, or obvious hæmolysis in one specimen of a batch, but in the statistical analysis these values have been taken into consideration

The levels of serum acetylsalicylic acid are obtained from the differences between aliquots of serum at each time, one aliquot is estimated for free salicylate, the other for total salicylate after hydrolysis by caustic soda

At the conclusion of the experiment random samples were taken from each of the original batches or tablets and analysed for total salicylate content The variation in content between tablets in the same batch was of the order of five per cent and there was no consistent difference between the aspirin content of the different groups

All venepunctures and all salicylate determinations were done by myself, thereby ensuring standard technique at all stages

Results

Results are shown in tables I and II The scatter between the values for each subject (figures in parentheses) mainly represents individual variation in the subjects themselves, since the variation due to the method was found to be usually less than 0 5 mg per 100 ml

Serum salicylate levels were much the same (table I) after taking bufferin, soluble aspirin *B P*, and paynocil, but considerably lower after taking aspirin *B P* The difference was significant at the 1% level at all times if aspirin is compared with the other three groups combined (see figure)

Plasma levels for acetylsalicylic acid differ little for the four aspirin preparations given (table II) The fact that they are all relatively low might be explained by partial failure of the fluoride present in the anticoagulant to inhibit the serum esterase concerned Lester et al (1946) found that an average of 25% of the total salicylate was present as acetylsalicylic acid The proportion found here varied from 10–25% approximately

TABLE II—MEAN PLASMA-ACETYLSALICYLIC-ACID VALUES (MG %)

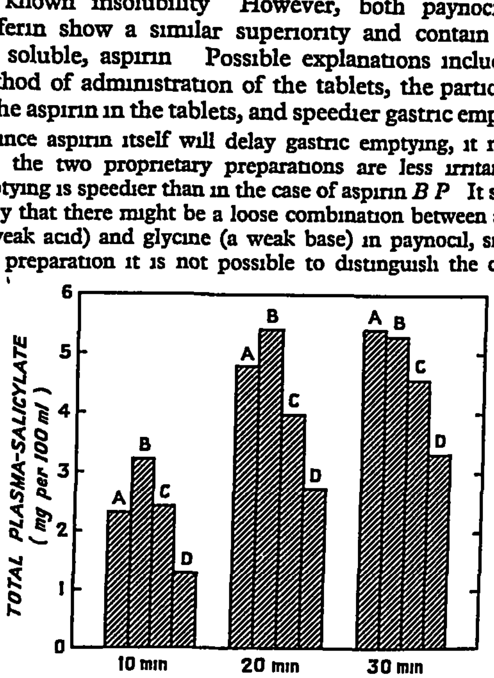
—	A Bufferin	B Soluble aspirin *B.P*	C Paynocil	D Aspirin *B P*
10 minutes	0 5 (0–1 1) 6	0 3 (0–0 8) 6	0 5 (0–1 7) 4	0 2 (0–0 9) 5
20 minutes	0 9 (0–1 6) 6	0 6 (0–1 4) 5	1·0 (0 2–2 1) 5	0 5 (0–1 1) 6
30 minutes	0 5 (0–1 2) 4	0 3 (0–1·0) 6	0·9 (0 1–2 1) 5	0 8 (0–1 3) 6

Range in parentheses Number of observations below

Discussion

Judging by evidence from blood-levels, plain aspirin has been shown to be roughly half as rapidly effective as soluble aspirin This difference might be expected from its known insolubility However, both paynocil and bufferin show a similar superiority and contain plain, not soluble, aspirin Possible explanations include the method of administration of the tablets, the particle size of the aspirin in the tablets, and speedier gastric emptying

Since aspirin itself will delay gastric emptying, it may be that the two proprietary preparations are less irritant and emptying is speedier than in the case of aspirin *B P* It seemed likely that there might be a loose combination between aspirin (a weak acid) and glycine (a weak base) in paynocil, since in this preparation it is not possible to distinguish the characteristic taste of aspirin on the tongue, but chromatographic analysis of solutions of these two components gave no support for this theory In the case of bufferin the present results confirm those of Paul et al (1950) and are at variance with those of Cronk (1958) and Batterman (1958) who found no difference between bufferin and a rapidly disintegrating proprietary aspirin



Total plasma-salicylate levels at intervals after 10-grain doses of aspirin by mouth A = bufferin, B = soluble aspirin *B P*, C = paynocil, D = aspirin *B P*

The presence of acetylsalicylic acid in the serum has been demonstrated again (Lester et al 1946, Smith 1951, Mandel et al 1954) Normally, significant quantities of the drug remain only for two to three hours (Gross and Greenberg 1948), because of its rapid hydrolysis to sodium salicylate by serum esterase The fact that aspirin is more diffusible than plain salicylate, because less of the former is protein-bound in the serum, probably explains the therapeutic superiority of aspirin over plain salicylate The clinical corollary of this is that, if aspirin is to be used logically it should not be said to be ineffective unless it has been taken at short intervals (i e , two- or three-hourly) This is particularly important in the relief of long-continued pain as in rheumatoid arthritis

The present trial demonstrates that under standard conditions calcium aspirin *B P* was as effective in giving rapid blood-levels as two proprietary buffered aspirins (paynocil and bufferin) but that all three were superior to plain aspirin *B P* The relative costs to the hospital service of these three drugs are

Aspirin *B P* = *0 12d for 10 grains aspirin*
Soluble aspirin *B.P* = 0 22*d* ,, ,, ,, ,,
Buffered aspirin (paynocil) = 0·54*d* ,, ,, ,, ,,
,, ,, (bufferin) = 1 1*d* ,, ,, ,, ,,

The superiority of calcium aspirin over plain aspirin in the rapid achievement of demonstrable blood-levels is stressed If in addition account is taken of the evidence incriminating plain aspirin as a cause of serious side-effects such as gastrointestinal hæmorrhage (Muir and Cossar 1955), its continued use appears questionable

Summary

Blood-levels of acetylsalicylic acid and salicylate obtained at 10, 20, and 30 minutes after gr 10 doses of aspirin *B.P*, soluble aspirin *B.P*, and two buffered preparations paynocil and bufferin were compared

Soluble aspirin *B P* gave approximately twice the blood-levels of aspirin *B P* at these times and equal levels were obtained with paynocil and bufferin, both of which were similarly superior to plain aspirin *B P* Suggested explanations are diminished local irritation and consequent speedier gastric emptying when soluble or buffered aspirins are used

The presence of unchanged acetylsalicylic acid is again demonstrated in serum and the significance of this discussed, with particular reference to the point that aspirin therapy cannot be said to have failed unless the drug has been taken at two- or three-hourly intervals

I am grateful to Dr Kenneth Robson, who originally suggested the study, and to Dr J C. Batten, for advice and encouragement, to Prof J Knowelden for help with the statistical planning of the trial, and to Mr G Franglen for carrying out the chromatography and assisting with the statistical calculation

I wish to acknowledge a grant from the research committee of St. George's Hospital towards expenses

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BISALBUMINÆMIA

A HEREDITARY ALBUMIN ABNORMALITY

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Knedel (1957, 1958) reported an abnormal protein in the serum of a 15-year-old girl with hepatitis Her sister, her mother, her maternal grandmother, and a maternal uncle all had a similar anomaly The sera from two cousins (a daughter and son of the uncle) did not contain demonstrable amounts of the anomalous protein From its electrophoretic and immunological behaviour, Knedel thought the protein was an albumin Other families with a similar anomaly have been reported by Nennsteil and Becht (1957), Wuhrmann (1958), Bennhold, Ott, and Scheurlen (1958) and Earle, Hutt, Schmid, and Gitlin (1958, 1959)

Case-report

A boy of 16 was seen in the skin department of King's College Hospital last August, with a curious condition of the hands These had always been cold and blue even in summer In the previous three years there had been an increasing flexural deformity of the fingers—first of the little fingers, and later, to a lesser degree, the ring, middle, and index fingers of one hand It was difficult to account for his inability to straighten these fingers there was no sclerosis of the skin, nor, apparently, any involvement of fascia or tendons The horny layer over the knuckles was slightly thickened and a slight mosaic of hyperkeratosis could be seen in the nailfolds The condition was clearly not acrosclerosis nor any form of Raynaud's phenomenon The boy's father had similar hands but could straighten his fingers normally The paternal grandfather (deceased) was said to have had cold blue hands

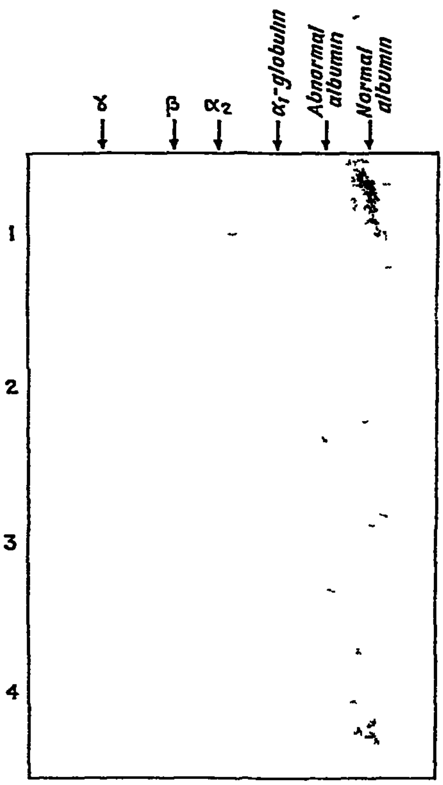

Fig 1—Electrophoretic demonstration of second component in region of albumin

Investigations

In the course of various laboratory investigations paper-electrophoretic analysis of the serum proteins revealed, in both father and son, a distinct double band in the region of the albumin The sera were submitted to an independent laboratory for confirmation and further study There, among other investigations, electrophoresis was carried out on filterpaper and in agar against known albumin controls and by the classical moving boundary method of electrophoresis The presence of a second component in the region of the albumin was confirmed (fig 1) Sera from the other members of the family were collected and examined As in the family reported from America, the genetic pattern (fig 2) seems to be that of a dominant heterozygote

We have assumed that the faster of the two " albumin " components is that normally seen in electrophoretic analysis We believe that the second peak represents an albumin, for the following reasons

1 (*a*) Zone electrophoresis on paper, cellulose acetate, and agar all displayed a well-defined double band having a mobility similar to that of albumin and faster than that

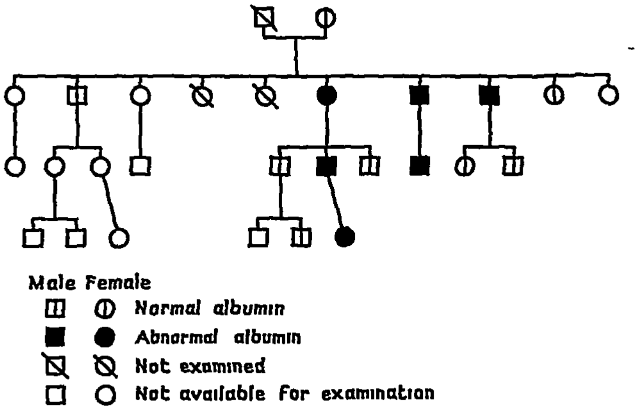

Fig. 2—Pattern of inheritance.

of the α_1-globulin in the control normal serum. Moreover α_1-globulin could be identified, clearly separated from the abnormal "albumin", having a mobility similar to the α_1-globulin in the control serum.

(b) When the serum proteins were subjected to moving-boundary analysis in 0·2 M phosphate buffer at pH 8·0 for six hours, a well-defined "hump" was seen on the posterior slope of the albumin peak, the α-globulin being clearly discernible behind it (fig. 3). The "hump" was constant on prolonged electrophoresis, its mobility being within the range of normal albumin.

2. When the serum proteins were exposed in buffered aqueous solution to *n*-tolyl-α-naphthylamine-8-sulphonic acid, a dye believed to couple specifically with albumin (Weber and Lawrence 1954), electrophoretic analysis showed that both "albumin" bands had coupled with the dye and that none of the other serum proteins present produced a fluorescent-coupled compound in this manner. Moreover the behaviour of the abnormal component with sulphonphthalein dyes also paralleled that of normal albumin (Franglen 1958).

3. The two components were separated by electrophoresis on starch block (Kunkel and Trautman 1959). Comparison of the two components by immunological techniques showed no difference between the two "albumins" nor between them and normal human albumin (fig. 4).

Discussion

This is the first family to be described in this country displaying this unusual serum-protein anomaly—the eighth, so far as we can ascertain, in the world literature. In none of the other families has the anomaly been shown to be associated regularly with any other demonstrable defect, most of the members being in perfectly good health.

In the present family the peculiar dermatological condition was noted in father and son. There is evidence that the grandfather also suffered from "cold blue hands". As we could not demonstrate the split albumin in the grandmother, it is reasonable to suppose that this defect was transmitted through the grandfather. While it is tempting to link the unusual skin condition with th protein abnormality, we must admit that four othe members (two female and two male) showing the spli albumin had no dermatological defect.

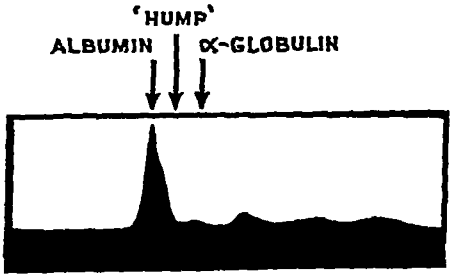

Fig. 3—Hump on posterior slope of albumin peak.

Preliminary studies have shown no striking deviation in the aminoacid analysis of the abnormal albumin. I we assume that the shape and size of this component doe not differ markedly from normal albumin, the electrophoretic analyses suggest that the net surface charge o the molecule is very near to that of normal albumin.

Bergstrand and Czar (1956, 1957) described a protei migrating between albumin and α_1-globulin in the seru from fœtuses up to the 19th week, obtained from legal abortions. They reported this component to be abou 10% of the normal albumin present. Such quantitative studies as we have made suggest that the abnormal albumin which we are now describing represents about 50% o the total albumin and that this proportion is remarkably constant—a finding similar to that of Earle et al. (1959). In thalassæmia (another hereditary protein dyscrasia) the fœtal type of hæmoglobin persists in varying amounts in different members of the family. Though it is tempting to propose that our abnormal albumin represents a persistence of the fœtal component described by Bergstrand and Czar, the condition differs from thalassæmia in one striking respect—namely, that all the members of the family we have examined, extending through four generations, have shown the component at a level of 50% of the total serum-albumin or else none at all.

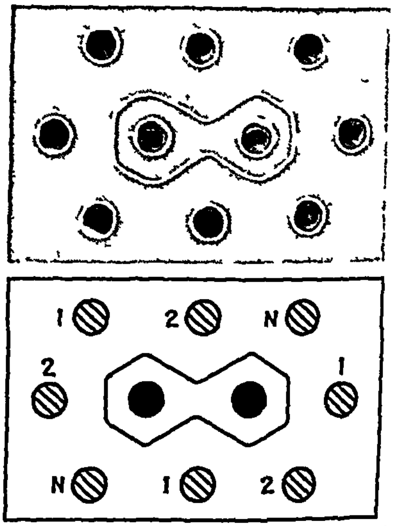

Fig. 4—Comparison of two "albumins" and normal human albumin.

Summary

In a family followed through four generations a bifid albumin occurs as a dominant heterozygous character. Reasons are given for regarding the abnormal component as albumin, and a comparison is drawn with thalassæmia.

In three successive generations an unusual skin condition was observed in three of the seven members of a family believed to be suffering from the protein dyscrasia.

G. Franglen and N. H. Martin acknowledge with gratitude financial support from the free funds of St. George's Hospital.

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THE THORN IN THE FLESH

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IN 1787, two years after publishing An Account of the Fox-Glove and Some of its Medical Uses, William Withering, writing about *Prunus spinosa* (blackthorn or sloe-tree) noted that "the thorns have something of a poisonous nature in the autumn." In 1801 he confirmed this observation. "From some effects which I have repeatedly observed to follow the prick of the thorns, I have reason to believe there is something poisonous in them."

I have recently observed and treated ten patients with this injury. No other similar series has been reported in English.

Most of the patients were agricultural workers, and, as might be expected, all the injuries were in the hand. There was no particular seasonal incidence.

The average interval between time of injury and first visit to the accident service was 8.7 days, and the average duration of outpatient treatment was 45 days. By comparison, 60 patients with other thorn injuries—e.g., rose, hawthorn, gooseberry, &c., or unspecified—were treated as out-patients for an average of 11.9 days.

Illustrative Case

A 67-year-old thatcher injured his left index finger with a blackthorn at the end of January, 1958. Next day "the finger started swelling and throbbing," and on the day after that his doctor started him on a week's course of tetracycline. At the end of the week he was able to resume work, but 2 days later his symptoms recurred and he was given intramuscular penicillin one mega-unit daily for 7 days. "The finger settled and the swelling went down", but symptoms returned when he had been back at work for 2 days.

After a sleepless night he was first seen by us on Feb. 13. He did not look ill and was apyrexial. His left index finger showed minor occupational scarifications in addition to the blackthorn puncture wound on the flexor aspect of the proximal interphalangeal joint. Swelling and tenderness were greatest over the proximal flexor pulp, there was no lymphangitis or lymphadenitis.

Under general anæsthesia the proximal pulp space was explored. The flexor tendon sheath proved to be thickened and tense. The sheath was opened, its thin yellow contents were evacuated, together with some "melon-seed bodies", and the granulomatous material associated with the thickened tendon sheath was excised. Skin sutures were inserted and the finger splinted with a plaster slab.

The contents of the tendon sheath showed many pus cells and occasional gram-positive cocci. No acid-fast bacilli were seen (Ziehl-Nielsen). Culture gave a light growth of micrococci and diphtheroids but no tubercle bacilli. The granulomatous material was described as "vascular granulation tissue with a dense polymorphonuclear exudate."

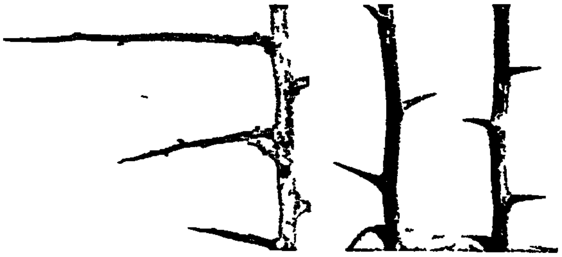
The patient was not ready to start mobilising the finger until March 4. By May 15 he could bring the index fingertip to within a centimetre of the base of the thenar eminence, and he was encouraged to return to work. He improved further during the next 10 weeks and was discharged.

This case is fairly typical. Some of our other patients, with more superficial injuries, required a shorter course of treatment, especially if referred to us early. The swabs revealed penicillin-resistant *Staphylococcus aureus* in three patients and penicillin-sensitive *Staph. aureus* in two, no other pathogen was isolated. One of our patients did not get antitetanus prophylaxis and developed tetanus of moderate severity. This might have happened after any penetrating wound sustained on a farm. None of the ten patients showed signs of bone infection or "bone tumour."

The patient described in the case-report twice collected blackthorns for us and delivered them in a sterile package, he obtained the specimens from the place where he sustained his injury. These thorns were cultured. The first specimen yielded an aspergillus, but saprophytic mycobacteria or actinomyces were not isolated. Subcultures of the second specimen yielded only aerobic spore-bearers and micrococci at 22°C and 37°C.

Discussion

Cactus spines, being organic material, can produce a foreign-body granuloma which may require surgical attention (Boyd 1956). Maylan (1952) recorded that certain plant thorns—e.g., rose and yucca—"in or near bone can cause a reaction in this tissue which may simulate a neoplasm or granuloma." Uteau and Bouget (1928) reported that in the Basque country the peasants attribute peculiarly noxious effects to the prick of the thorns of certain shrubs. These authors noted that two acquaintances had tetanus after thorn wounds. Also they held that the fly-infested putrefying bodies of birds and small animals spitted on these thorns by shrikes and other birds stocking their larders accounted for the inflammation after the thorn pricks. They compared these infections to those following an "anatomical prick" in the post-mortem room or the serious finger infections endemic among the cod-fishers of Newfoundland. (Presumably they were referring to "fat finger" or "seal finger", a condition well described by Candolin [1953].) Dr. G. Taylor, director of the Royal Botanic Gardens at Kew, told me that a member of his staff had noted that "shrikes often impale their 'kills' on the thorns of blackthorn and that this might conceivably cause some sort of bacterial infection." Brimble (1949) pointed out that "these thorns easily snap at their tips, which explains why in some rural areas the blackthorn is supposed to be poisonous, because when the thorn penetrates the skin the tip breaks off and becomes embedded in the flesh and festering ensues." Some of the differences between the thorns of the blackthorn and hawthorn are apparent in the figure.



The smooth short needle-sharp spine of the hawthorn (right) is in sharp contrast to the rough long brittle thorn of the blackthorn (left)

We inquired of Dr. J. W. Fairbairn, reader and head of the department of pharmacognosy, University of London, and Dr. W. O. James, F.R.S., professor of botany, Imperial College, London, regarding the "poisonous nature" of these thorns, but neither was aware of any toxic substance that had been isolated from them.

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* This work was done while the author had a research grant from the Nuffield Provincial Hospital Trust. Present address: Orthopædic Division, Toronto General Hospital, Toronto, Canada.

Summary and Conclusions

1 In ten blackthorn injuries of the hand the average interval between time of injury and reference to the accident service was 8 7 days, and the average duration of outpatient treatment was 45 days

2 Sixty other patients with various thorn injuries seen during the same period required outpatient treatment for an average of 12 days

3 Bacteriological examination of these blackthorn wounds revealed penicillin-resistant staphylococci in three patients and penicillin-sensitive staphylococci in two, no other pathogens were isolated One patient developed tetanus of moderate severity Cultures of blackthorns obtained from hedges yielded no specific pathogen Histological examination showed a non-specific granulomatous reaction

I am grateful to Mr J C Scott, director of the accident service, for his interest and help, to the members of the bacteriology department and in particular to Dr R L Vollum, bacteriologist to the United Oxford Hospitals, to Dr R H Cowdell, pathologist to the United Oxford Hospitals, to Mr B Juniper, of the School of Botany, University of Oxford, and to Mr E Tugwell of the photographic department, Radcliffe Infirmary

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CATHETER DRAINAGE AND INFECTION IN ACUTE RETENTION OF URINE

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IN a previous investigation of postoperative urinary infection, it was found that about a third of the patients who came for operations on prostate or bladder were already infected (Miller et al 1958) Most of these infected cases had been catheterised immediately after emergency admission with acute retention of urine Many of the organisms were resistant to antibiotics, which indicated that they originated in the hospital and that in all probability the patients had acquired the infection as a result of catheter drainage, having entered the hospital with sterile urine Air bubbles which ascended in the drainage tube were found to carry bacteria to the bladder and to constitute an important cause of infection

In the same investigation, it was shown that the use of closed aseptic bladder drainage reduced infection after prostate operations, and so it seemed obvious that the same principle could be applied to bladder drainage in cases of acute retention of urine In such patients, bleeding is ordinarily no problem so that no provision is needed for washing out the bladder

Methods

In 1957 a simple closed-drainage apparatus was introduced which could be sterilised and kept ready for use in the wards It was then used in a controlled trial on patients with acute retention of urine who were admitted as emergencies to the Bristol Royal Infirmary from February, 1958, to April, 1959, and to Southmead Hospital from October, 1958, to April, 1959 Altogether, 118 patients with acute retention were treated by continuous bladder drainage, 100 had sterile urine initially and these were the subjects of our investigation Most of them came to operation after periods of drainage varying from one day to several weeks, but a few were discharged without operation. For practical reasons a completely random choice of admissions could not be made, so patients admitted under the care of some surgeons were catheterised and connected to an open-drainage system, while the remainder had the special closed-drainage system connected

For open drainage, a piece of boiled rubber tubing three feet long was attached by a sterile glass connection to the catheter with the free end hanging over the side of the bed into an open bucket or urine bottle The closed-drainage apparatus (fig 1) consisted of a Winchester bottle (2-litre capacity) through the rubber stopper of which two holes were bored. A glass tube through one hole dipped below the surface of 100 ml of liq formaldehyde *B P C* in the bottom of the bottle The other hole was left as an air outlet The glass tube with the rubber stopper was boiled for three minutes before assembling the apparatus The formalin served not only to sterilise the inside of the clean bottle by the overnight action of its vapour, but also as a disinfectant air trap to prevent any bacteria which might enter through the air outlet from reaching the drainage tube alive, and also to prevent the passage of air bubbles up the tube A tablet of paraformaldehyde (' Formagene ') was placed on the top of the stopper, which was then covered with a ' Cellophane ' bag to maintain the sterility of the upper end of the tube prior to use For fluid-balance records, a printed volume scale was attached to the outside of the bottle For use the cellophane bag was removed and, with aseptic precautions, the catheter was connected to the glass inlet tube of the bottle by means of a boiled rubber tube When a bottle became full, it was replaced, with careful asepsis, which included clamping the tube near its lower end to prevent the ascent of air bubbles Urine was taken for examination when the catheter was first inserted, and afterwards daily by means of a sterile needle inserted into the tube, as previously described.

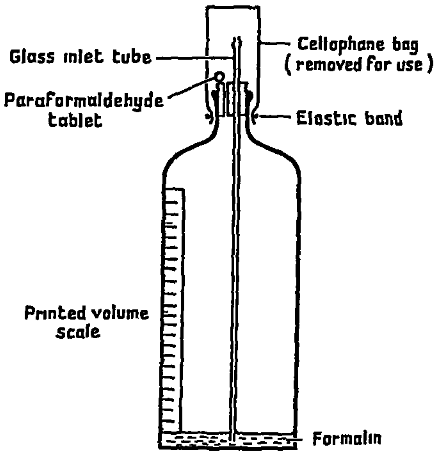


Fig 1—Apparatus for closed aseptic drainage of the bladder, when irrigation is not required

The bacteriological methods and the diagnostic criteria of infection were the same as before

Results

Of the 100 patients admitted with sterile urine, 15 were excluded from the trial for the following reasons (*a*) 7 either had an operation performed or died within twenty-four hours of admission, (*b*) 4 had prophylactic antibiotics, or (*c*) 4 required repeated catheterisation during the first few days (and all became grossly infected during this time)

Of the remaining 85 patients, 26 were treated with open drainage and 49 with closed drainage, while in a further 10 who started with closed drainage asepsis was broken by the

TABLE I—INCIDENCE OF URINARY INFECTION IN PATIENTS WITH ACUTE RETENTION OF URINE, TREATED BY OPEN BLADDER DRAINAGE AND BY CLOSED ASEPTIC DRAINAGE

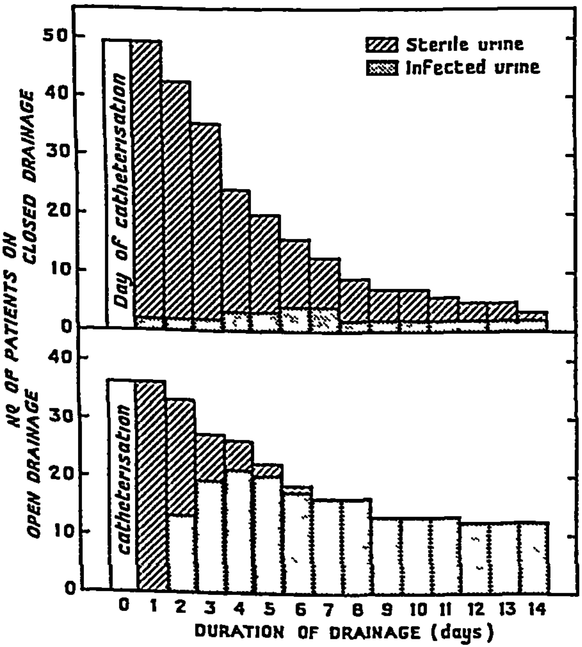
Drainage	Patients	
	Total	Infected
Open	26	19 (73%)
Closed	49	5 (10%)*
Closed but disconnected	10	9 (90%)

* 2 of these patients became infected within eighteen hours of inserting the catheter, probably as a result of the catheterisation and not of subsequent retrograde infection.

disconnection of the drainage tube which was then temporarily blocked by a wooden spigot for such reasons as visits to X-ray department, bathing, and getting up to sit in a chair. The nursing staff did not appreciate at first that the closed-drainage system, once established, must never be disconnected, but since the startling incidence of infection in these cases has been observed there has been no difficulty in maintaining the closed system. Table I shows the incidence of infection, by organisms other than *Staphylococcus albus*, during continuous drainage in this group of 85 patients. The high infection-rate (9 out of 10) in patients who had their closed-drainage system disconnected is notable and emphasises the danger of acquiring infection from spigots, blankets, pyjamas, &c.

Time of Onset of Infection

On open drainage infection usually developed quickly, whilst on closed drainage survival without infection was the rule even when the drainage was continued for many days (fig. 2). Of the 5 patients on closed drainage who did become infected, 2 developed their infections within eighteen hours of catheterisation, probably as a result of the insertion of the catheter and not of subsequent retrograde infection. None of the 10 patients whose closed drainage was inadvertently disconnected survived infection for more than two days afterwards.



* Includes 10 patients whose closed drainage was inadvertently disconnected.

Fig. 2—Urinary infection following insertion of indwelling catheters, in relation to method of draining the bladder.

Nature of Infection

In our hospitals, most urinary infections after prostate operations are caused by "hospital organisms" with abnormal antibiotic sensitivities (Gillespie 1956). Similar organisms caused infection in the cases described above (see table II).

Discussion

In all catheter drainage systems, after the initial catheterisation has been achieved without infection the chief dangers are contamination of the end of the catheter by disconnection, and by bacteria conveyed by air bubbles which rise up the drainage tube from the open end. This latter hazard can be avoided by using a closed system with an antiseptic fluid seal in the collecting bottle.

TABLE II—ANTIBIOTIC RESISTANCE OF BACTERIA IN INFECTIONS COMPLICATING CATHETER DRAINAGE OF ACUTE RETENTION OF URINE

Organisms	Total infections	Antibiotic sensitivities
Streptococcus fæcalis	7	
Staph. aureus	6	1 sensitive and 5 resistant to penicillin. 4 also resistant to sulphonamides, streptomycin, and other antibiotics
Coliform bacilli	8	All resistant to sulphonamides and streptomycin
Proteus species	10	All resistant to sulphonamides and streptomycin. 9 also resistant to other antibiotics
Pseudomonas pyocyanea	2	1 sensitive and 1 resistant to sulphonamides, streptomycin, chloramphenicol, and oxytetracycline
Other gram-negative bacilli	4	All resistant to sulphonamides, streptomycin, and oxytetracycline
Total	37	28 organisms with abnormal antibiotic resistance

Infections by *Staph. albus* are not included.

So many complications of prostate operations are due to infection that every effort should be made to prevent infection both before and after operation. Bacteria which are allowed to invade the urinary tract are potential causes of lethal bacteræmic shock, septicæmia, or pyelonephritis (Ezzo and Knight 1957, Slade 1958, Miller et al. 1958). In recent years, emergency prostatectomy has been advocated as the best treatment for acute retention because it avoids preliminary catheter drainage with its inevitable risk of infection. In our experience emergency prostatectomy for acute retention can produce excellent results because of the sterile operation field which can be maintained, but there is also little doubt that if one can avoid infection by other means and so enable the operation to be done at a reasonable hour with the same chance of maintaining sterile urine, one may also avoid other hazards incidental to emergency surgery performed at a late hour of night. The ease with which these cases become infected is demonstrated by the results in the group in which the catheter was disconnected. To be effective, therefore, the drainage system must be kept closed for the whole period of drainage.

The same system could be used for continuous drainage of the bladder in other conditions.

Summary

A controlled trial of a simple closed aseptic drainage apparatus for use after catheterisation for acute retention of urine is described.

The apparatus can be cleaned, sterilised, and kept ready for use in the ward.

Its use in the treatment of patients with acute retention of urine enabled sterility of the urine to be maintained in the great majority of cases, until they came to operation. With open drainage, most patients quickly became infected.

We thank the board of governors of the United Bristol Hospitals and the management committee of Southmead General Hospital for grants towards the cost of this research, and the ward sisters for their enthusiastic assistance.

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THE DIURETIC EFFECT OF SPIROLACTONE SC-9420 IN A CASE OF SECONDARY ALDOSTERONISM

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Kagawa et al. (1957) and Liddle et al. (1957) reported that synthetic steroids—the spirolactones designated SC-5233 and SC-8109—block the renal effects of aldosterone and deoxycortone (desoxycorticosterone) in adrenalectomised animals and patients with adrenal insufficiency. In the absence of sodium-retaining hormones the drug had no effect.

The magnitude of the response was directly related to the dose of steroidal spirolactone and inversely related to the dose of sodium-retaining substances given. Therefore the blocking effect was thought to result from competitive inhibition, probably at the level of the renal tubules.

When a high urinary output of aldosterone was induced in normal subjects by feeding a low-sodium diet, spirolactones had the same effect as in patients with Addison's disease who were receiving deoxycortone. The drugs were also given to a number of patients with œdema due to congestive heart-failure, who, as was observed by Deming and Luetscher (1950), excrete large amounts of sodium-retaining substances in the urine. Most cases responded with increase in sodium and water excretion and no change or reduction in the excretion of potassium. The observed reduction in the excretion of titratable acid and ammonia is regarded as further evidence that steroidal spirolactones act as specific aldosterone inhibitors (Liddle 1958).

Kerr et al. (1958) gave SC-8109 by intramuscular injection to three patients with liver cirrhosis and ascites. A sodium and water diuresis occurred in two; potassium output and body-weight did not change.

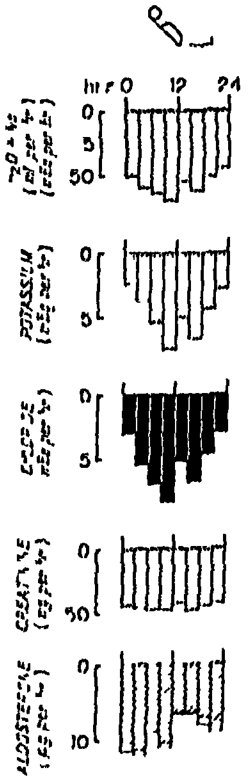

Fig. 2—Diurnal excretory rhythm. Experimental conditions as described under fig. 3. Sodium output was less than 1 mEq. per day, too small to be depicted. Both results of duplicate determinations of aldosterone are given.

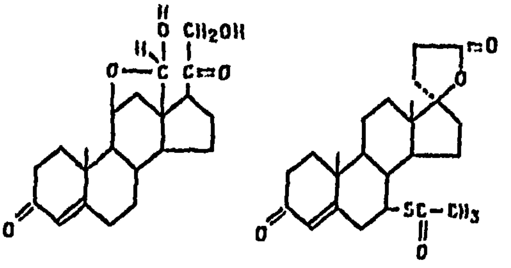

Fig. 1—Chemical formulæ of aldosterone and the steroidal spir lactone SC-9420.

Unfortunately these spirolactones have to be give parenterally in microcrystalline suspensions or oil solutions, the effective oral dose being 30–60 times th parenteral dose.

We have used a new spirolactone SC-9420 (fig. 1) o which no clinical data have hitherto been availabl. I

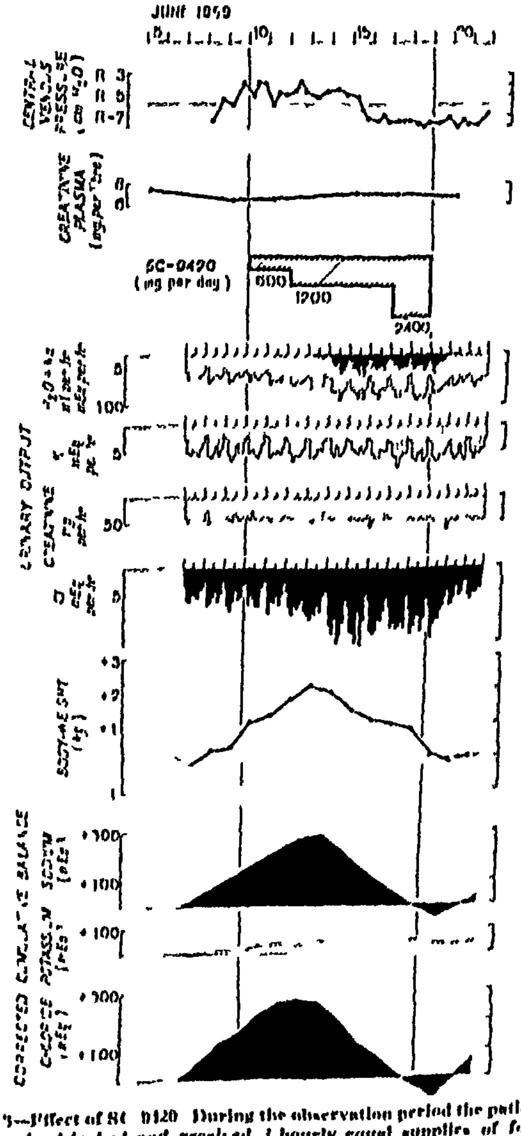

Fig. 3—Effect of SC-9420. During the observation period the patient remained in bed and received 3-hourly equal supplies of food providing 1710 calories, 57 mEq. Na, and 85 mEq. K daily, and drugs making a total of 30 g. urea, 48 mEq. KCl, 81 mEq. NH_4Cl, 0.1 mg. digoxine, 16 mg. thyroid, and 4 µg. triiodothyronine daily.

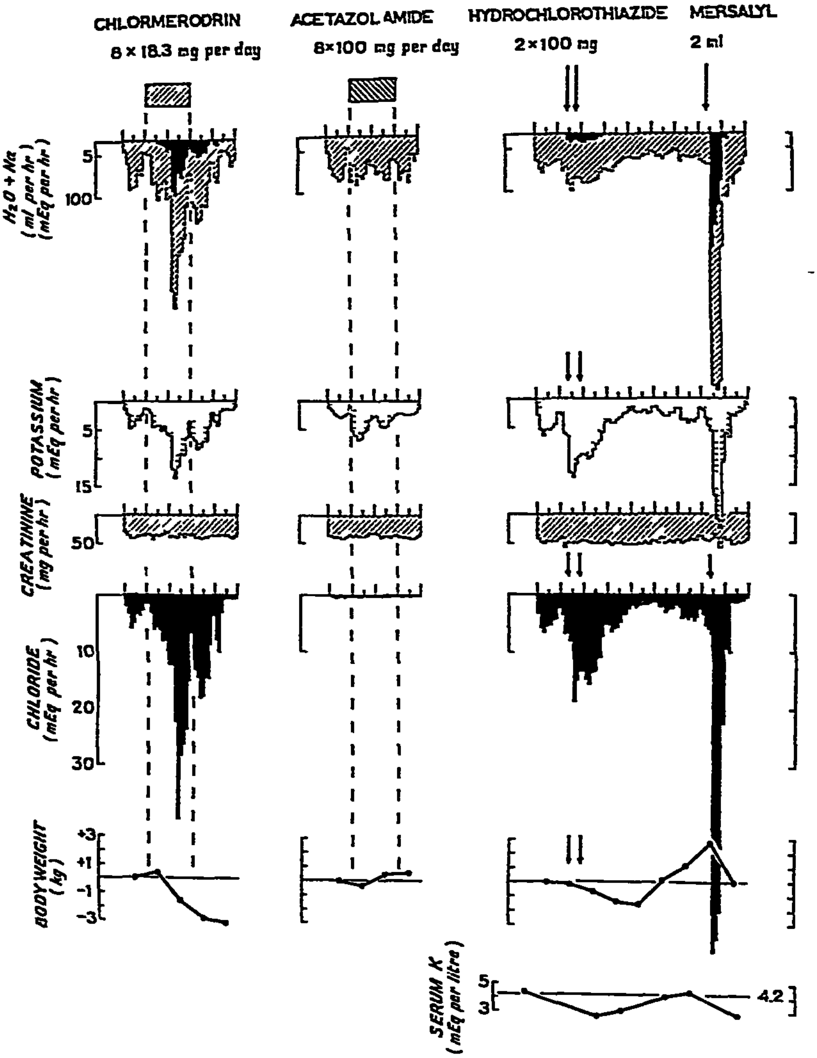

Fig 4—The effect of four diuretics. Same legend as in fig 2. $CaCl_2$ was given instead of NH_4Cl during the treatment with chlormerodrin, and no KCl and NH_4Cl was given during the treatment with acetazolamide

can be given by mouth. The makers claim that its dose-response relation is better than that of the earlier spirolactones We tested it in a proven case of secondary aldosteronism and compared the pattern of diuresis with that induced by other diuretics

Investigation

The patient, a highly cooperative man of 29, has severe chronic heart-failure due to rheumatic mitral stenosis and incompetence with auricular fibrillation.

Previous History

He has been under our close observation for 6 years Treatment has been by a salt-free diet, digoxin, and mersalyl, with sufficient amounts of ammonium chloride, several times urea has had to be administered for many weeks to combat hyponatræmia. Gradual deterioration of cardiac function led in 1953 to inefficacy of even large doses of mersalyl This necessitated a total suppression of thyroid function with ^{131}I, after which the mersalyl became effective again. He is on a subliminal supply of thyroid powder, and his intake of salt and water is rigidly restricted. Moreover, he still needs ammonium chloride and injections of mersalyl to keep him free from œdema. For 6 years he has not excreted any sodium except on the days that mercurial diuretics were given. Renal function is unimpaired. On rigid fluid restriction urine osmolarity rises to 1200 milliosmol per litre Creatinine-clearance is about 120 ml. per minute (more than 50 determinations)

Unfortunately increasing symptoms of hypersensitivity to mersalyl have developed. We have therefore tried the effect of other diuretics on water and electrolyte excretion under the rigorously standardised conditions described in previous papers (Borst and de Vries 1950, Borst 1954)

Observations without Spirolactone

The patient was kept in bed on an intake of 57 mEq daily The urine was collected in 3-hour periods and analysed for sodium, chloride, potassium, and creatinine. Under these conditions even small changes in the pattern of diuresis can be distinguished. Body-weight and arterial and central venous pressure (method of Borst and Molhuysen 1952) were recorded daily, serum electrolytes, hæmoglobin, and plasma creatinine at regular intervals A corrected cumulative balance of sodium, potassium, and chloride was calculated as described by Molhuysen et al. (1950)

Using the method of Moolenaar (1957, 1958) we found a urinary excretion of 205–310 microgrammes aldosterone per day, whereas the normal values for persons on a normal salt intake are 3–13 microgrammes During one of the experiments the patient excreted on a control day more aldosterone in a 3-hour period than normal persons excrete during the day The highest aldosterone output was between midnight and noon (fig 2)

Effects of Spirolactone

Fig 3 shows that in the control period no sodium was excreted The cumulative sodium balance was positive, and the body-weight and central venous pressure rose After the dosage of spirolactone had been increased to 1200 mg per day sodium output started, and it is noteworthy that the excretion pattern of sodium followed the normal diurnal rhythm The cumulative sodium balance changed from about +300 mEq to zero Chloride output had the same pattern The influence on the potassium excretion was insignificant. However in the period when the sodium balance was negative the (corrected) cumulative potassium balance showed a slight positive trend The excretion of creatinine and the creatinine-clearance were unaffected. Increasing the dose of SC–9420 to 2400 mg per day for 2 days had no additional effect

With the small supply of SC–9420 available the treatment could not be continued After it was abruptly stopped the sodium output took at leat 36 hours to return to the zero level

The levels of serum electrolytes remained constant during the experiment, nor did the arterial pressure and pulse-rate change. The body-weight and the central venous pressure rose and fell parallel with the sodium balance. At the peak of retention the patient was uncomfortable and dyspnœic, and he benefited greatly from the diuretic effect of the spirolactone. The only side-effect noted was slight drowsiness

The excretion pattern of aldosterone and other adrenocortical steroids during the trial with sc-9420 could not be studied, because immediately after the beginning of the treatment at least two oxidation products of the steroidal spirolactone were excreted in the urine and interfered with the chromatographic separation of aldosterone and the Zimmermann colour reaction.

Fig 4 shows the renal response to several diuretics in the same patient under similar conditions It is clear that the effect of spirolactone sc-9420 differs from that of the diuretics quantitatively and qualitatively

Mersalyl provoked a large diuresis comprising water, sodium, chlorides, and potassium the effect started at once and lasted 24 hours Chlormerodrin, a mercury compound for oral use, showed the same pattern but the effect lasted longer The only effect of acetazolamide (' Diamox ') was an increased excretion of potassium Hydrochlorothiazide in high dosage gave a small sodium output, yet the sodium balance remained positive There was a very marked rise in the excretion of potassium. In spite of the 85 mEq potassium in the diet and the additional supply of 48 mEq potassium per day, the cumulative potassium balance became negative (balances not presented in fig 4) and the serum-potassium level dropped from 4 3 to 2 75 mEq per litre The diuresis was followed by a compensatory retention of potassium

Although the diuretic effect of sc-9420 is weaker than that of mersalyl, the results obtained in a short experiment suggest that the spirolactone by " selective chemical adrenalectomy " can also keep this patient in circulatory and electrolyte equilibrium, which non-mercurial diuretics could not achieve

Summary

The new spirolactone sc-9420 was tested under standardised conditions in a patient with heart-failure, who excreted large amounts of aldosterone in his urine and who for 6 years had not excreted sodium in the urine except when mercurial diuretics were given The spirolactone induced an appreciable sodium output, while the potassium output remained almost constant The characteristic excretion pattern could be distinguished from that produced with various other diuretics in the same patient Side-effects were unimportant

sc-9420 used in this trial was supplied by Messrs G D Searle We thank Prof A Querido (Leiden) for his instructions and help with the aldosterone determinations

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> " On admission he had been asked if his diet was normal and had replied yes After some time one of the physicians asked what exactly had he been eating, and when this question was put, the patient said he had been eating little more than bread, margarine and treacle during the last three years In asking the patient if his diet was normal, the questioner had wanted to know if his diet was suitable to maintain health, in saying that his diet was normal the patient had wanted to say that there had been no recent change from his usual diet This is an example where the questioner failed to obtain the information he required because different people attributed alternative meanings to the same word "—M L Johnson Abercrombie, *The Anatomy of Judgment*, p 106 London Hutchinson 1960

THE NATRIURETIC ACTION OF HEPARIN AND SOME RELATED SUBSTANCES[*]

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In an earlier paper (Majoor et al 1957) we showed that heparin has a diuretic action in patients with œdema of varied ætiology Moreover, in a man with coronary insufficiency without œdema or any other signs of heart-failure, sodium balance became distinctly negative and potassium balance slightly positive during intravenous heparin therapy The diuretic effect never appeared until after 36 hours of treatment, and did not reach a maximum until 3 days later When the heparin injections were discontinued, sodium excretion took about two days to return to its basal level In one patient potassium excretion was found to be increased in the first few days after stopping the drug The combination of natriuresis and potassium retention suggested that heparin might suppress the adrenal cortical function

Coumarin drugs did not increase sodium excretion in any of these patients

Since 1957 we have accumulated further evidence that heparin is a diuretic with a characteristic excretion pattern for sodium, often accompanied by slight potassium retention, and that it acts both in patients with œdema and in healthy persons (Majoor et al 1960) In this paper we report on the diuretic activity of the semisynthetic heparin congeners ' Thrombocid '[†] and Ro1-8307[‡] Thrombocid is an anticoagulant used in many German clinics Ro1-8307 is a heparinoid said to have low anticoagulant activity with relatively distinct clearing properties (Studer et al 1956, Reber et al 1959) Table I

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[*] We are indebted to the Organisation for Health Research, T N O, for a grant in support of this investigation

[†] Manufactured by Dr Benend K G, München-Solln, Germany

[‡] Ro1-8307, nr 36, was supplied by the Hoffmann-La Roche Laboratories Basle The drug is not yet commercially available

TABLE I—CHEMICAL AND PHYSIOLOGICAL PROPERTIES OF HEPARIN, Ro1-8307, AND THROMBOCID

—	Heparin	Ro1-8307	Thrombocid*
Chemical composition	Mixture of mucoitin polysulphates	N-formyl-chitosan polysulphuric acid	Xylan-poly-sulphuric acid
Source	Extracted from lungs or livers	Semisynthetic product of animal origin	Semisynthetic product of vegetable origin
Molecular weight	12,000–20,000	Approximately 5000	Approximately 3000
Sulphur content	10–14%	Approximately 15%	Approximately 14%
Carbohydrate part of molecule	Glucosamine and glucuronic acid	Acetyl-glucosamine	Xylose
Anticoagulant effect	+ + +	In humans far lower than heparin (on a weight basis)	40–45% of heparin (on a weight basis)
Clearing effect	+ + +	About 10% of heparin in humans About 12% of heparin in rabbits	+ +
Diuretic effect Daily dose necessary for diuretic action	+ + + 200–400 mg	+ + 400–800 mg	+ + 600–800 mg

* Details communicated by manufacturer

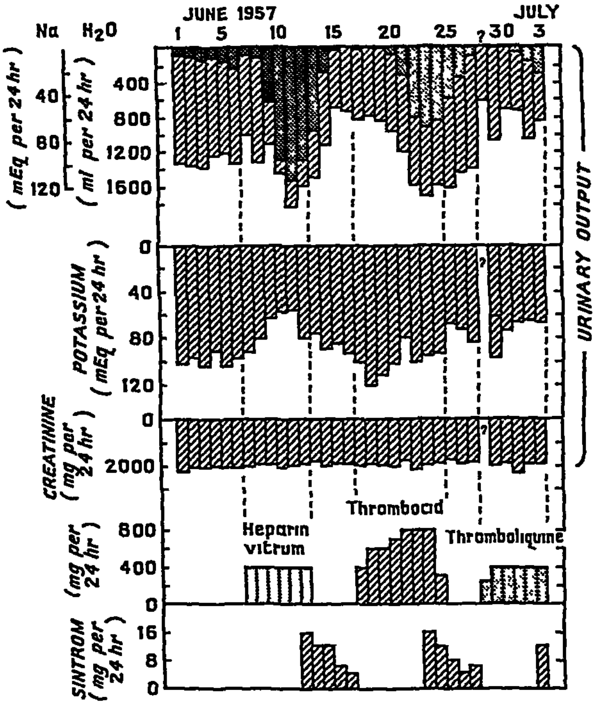

Fig 1—Diuretic response to two commercially available heparins and thrombocid in patient A

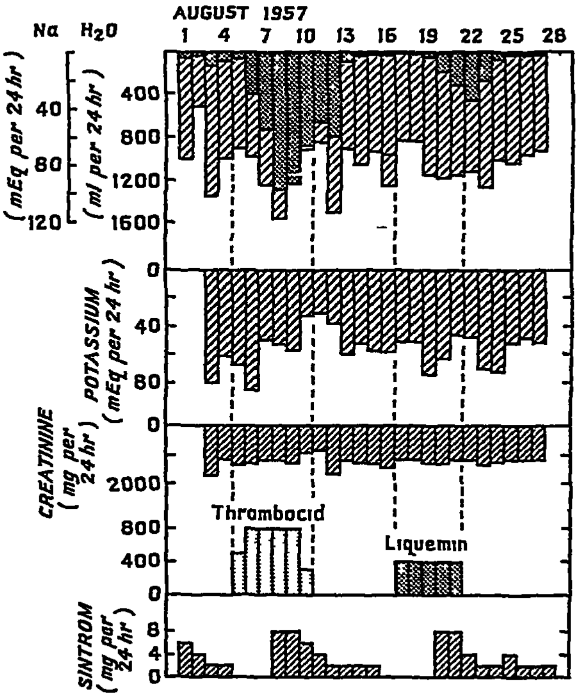

Fig 2—Diuretic response to thrombocid and the heparin liquemin in patient B

shows some chemical and physiological properties of the three polysaccharide sulphates used

Material and Methods

The diuretic action of heparin and the two heparinoids was studied in six patients—three with thrombosis of the legs, one with thrombosis of the brachial vein, one convalescent from bronchopneumonia, and one with a nephrotic syndrome Three or four intravenous injections were given each day, for 5–8 days in most patients The daily dose for patients A, B, D, and E is indicated in the figs 1–4 C and F received 300 mg of heparin daily for 4–6 days During a second period of investigation increasing amounts of Ro1-8307 were given (100–450 mg daily) to a total of 3000 mg over 15 consecutive days in patient C and 3000 mg over 8 days in patient F

As heparin and heparinoids are sodium salts of strong acids, we have determined the sodium content of the preparations used. We found 0·27–0·31 mEq Na+ per ml for all three drugs (1 ml contains 50 mg of the drug) Daily sodium intake was increased in this way with 1·5–2·0 mEq per 24 hours during heparin or Ro1-8307 therapy As thrombocid was given in doses up to 800 mg per 24 hours, these patients received a sodium increment of at most 5 mEq per 24 hours It is clear from figs 1–4 and table II that these small amounts of sodium could not be the cause of the enhanced sodium output found in our patients

Diets

Two kinds of diets were supplied to the patients

(*a*) The 24 hours were divided into eight periods At the beginning of each 3-hour period the patients drank a constant amount of milk and water, in most experiments supplemented by a fixed quantity of canned fruit-juice of one consignment, some biscuits, and in some cases a few grammes of cheese, always of the same lot. In this way the intake of fluid, electrolytes, and calories was kept constant. At the end of each period urine was collected and great care was taken to avoid loss During the observation the patients remained recumbent. This technique of examination was described by Borst and de Vries (1950)

(*b*) All foods and drinks were weighed and measured, and the daily ration was kept constant. The sodium content of these diets was low (about 10–20 mEq per 24 hours) To keep the potassium intake constant, canned vegetables of one kind and the same brand were used. Three meals were given each day Urine was collected over 24-hour periods All patients were weighed daily before breakfast.

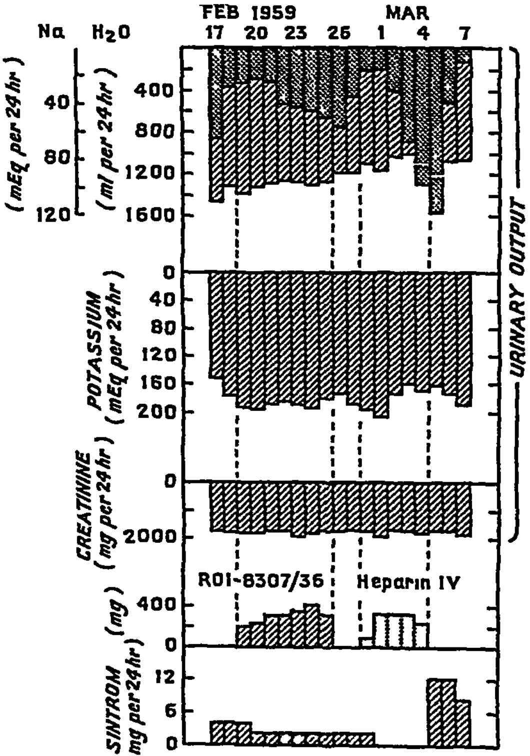

Fig 3—Diuretic response to Ro1-8307/36 and heparin in patient D

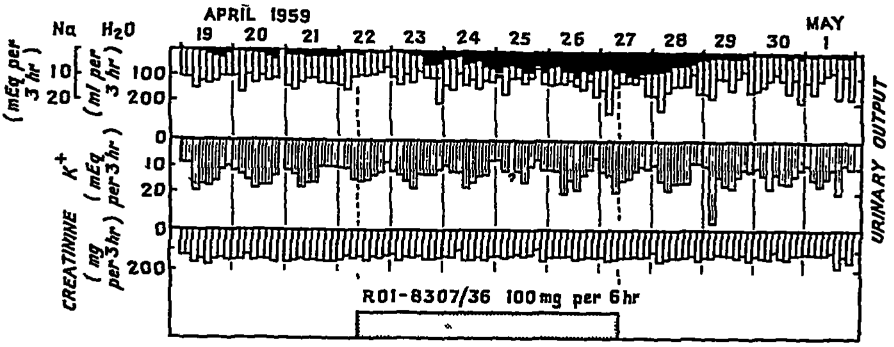

Fig 4—Diuretic response to Rol-8307/36 in patient E

Laboratory Methods

Sodium and potassium were determined by flame photometer To check the accuracy of urine collections creatinine was determined in all samples, using the alkaline picrate method For purposes of comparison the mean daily urinary excretion of water, sodium, potassium, and creatinine was calculated over short periods before, during, and after administration of the drug used To represent the period of treatment, the days with a maximal urinary sodium output were selected in most cases this was the 3rd to 5th day of drug administration To represent the period after drug administration, we chose the first days when pre-treatment levels of sodium excretion were regained—often the 3rd to 5th day after withholding heparin or heparinoids

Results are shown in table II and the figs 1–4

Results

All patients responded to heparin or heparinoids by an increase of urinary sodium excretion The pattern of this response is seen in figs 1–4 Sodium excretion did not increase until after 36 hours of therapy, and was maximal after 3–5 days At the same time potassium excretion decreased slightly or remained constant For 2–3 days after withdrawal of the drugs a slight increase in potassium excretion was noted in some cases, usually associated with a urinary sodium output lower than it was before treatment

Compared on a weight basis, thrombocid and Rol-8307 seem to be less potent diuretics than heparin

Discussion

As most of these results were obtained in patients with thrombosis, the natriuretic action of heparin might seem attributable to improvement of the circulation, caused by the action of heparin on the thrombotic process and the absorption of local œdema Against this explanation are the following facts

1 Coumarin drugs did not increase sodium excretion in any of our patients

2 Heparin had a distinct effect on sodium excretion in patients E and F who had no thrombosis

3 Rol-8307 has almost no influence on coagulation, but shares the natriuretic properties of heparin

4 During heparin therapy, slight retention of potassium was seen in most patients Borst (1954) has shown that circulatory diuresis is usually attended by potassium excretion

A diuretic pattern consisting in elimination of fairly large amounts of sodium (and chloride) with moderate amounts of water, and retention of potassium, points to the distal renal tubules as the site of action This excretion pattern is similar to that found in Addison's disease and can be reproduced by administration of amphenone (Renold et al 1957, Thorn et al 1957) and spirolactones (Liddle 1957) Hence it seems possible that heparin and the heparinoids (or their metabolites ?) act by reducing the output of aldosterone, as amphenone does, by blocking steroid action in the kidney, as suggested for the spirolactones, or by accelerating the destruction or

TABLE II—*MEAN URINARY EXCRETION OF WATER, SODIUM, POTASSIUM, AND CREATININE BEFORE, DURING, AND AFTER* TREATMENT WITH HEPARIN OR HEPARINOIDS

Patient	Sex and age	Clinical diagnosis	Œdema before treatment	Type of diet	Treatment	Body-weight (kg)		Days observation*			Mean urine vol in period mentioned (ml per 24 hr)			Mean sodium excretion (mEq per 24 hr)			Mean potassium excretion (mEq per 24 hr)			Mean creatinine excretion (mg per 24 hr)		
						Before treatment	After treatment	Before	During	After	Before	During	After	Before	During	After	Before	During	After	Before	During	After
A	M 34	Phlebothrombosis of right leg	Trace	b	Heparin	78 9	75 9	3	3	3	1260	1460	770	13	87	2	98	59	93	2040	2020	1930
				b	Thrombocid	75 6	75·0	3	3	2	770	1650	1260	2	66	6	93	97	91	1930	1990	1890
				b	Heparin	74 4	73 8	2	2		1260	980		6	20		91	67		1890	1870	
B	F 52	Thrombophlebitis of left leg Coronary insufficiency without heart-failure. Hypostatic œdema of both legs	None	b	Thrombocid	99 2	96 8	3	5	3	1080	1200	1090	7	73	2	70	43	57	1490	1260	1420
				b	Heparin	96 0	95 0	3	3	4	1090	1160	1000	2	24	3	57	53	57	1420	1280	1240
C	M 17	Phlebothrombosis of left brachial vein possibly of traumatic origin	None	a	Heparin	59·9	58 1	2 5	3	2	1640	1810	1730	28	86	28	84	78	87	1600	1660	1550
				b	Rol-8307	58 7	58 3	3	3		1620	1560		2	16		32	33		1530	1580	
D	M 46	Spontaneous phlebothrombosis of both legs	Trace	a	Rol-8307	70 3	70 2	3	3	2	1340	1260	1140	23	51	17	193	184	202	1800	1790	1050
				a	Heparin	70 6	?	2	3	1	1140	1120	1080	17	95	11	202	164	191	1850	1760	1870
E	M 56	Reconvalescent after bronchopneumonia. No œdema	None	a	Rol-8307	51·0	50 5	3	3	2	920	1030	1030	10	59	11	112	110	110	1170	1150	1080
F	F 22	Nephrotic syndrome, grossly œdematous	– + +	b	Heparin	63 7	62 6	3	3	3	840	960	950	4	24	3	83	73	81	1490	1520	1570
				b	Rol-8307	63 2	61 4	3	3		790	930		1	24		71	81		1460	1500	

* i e , number of days used for computation of mean outputs

elimination of aldosterone. These possibilities are being investigated (Cejka et al. 1960)

In sharp contrast to the action of mercurials, acetazolamide, and chlorothiazides, the diuretic action of heparin or the heparinoids never became apparent during the first 36 hours of therapy and never stopped within 48 hours of terminating intravenous administration. Though a late natriuretic response of the same type has sometimes been reported after amphenone and less definitely after spirolactone administration, in other experiments an immediate response was found (Renold et al. 1957, Thorn et al. 1957, Liddle 1957, 1958, Ross and Bethune 1959) As heparin and related substances without exception caused a delayed type of diuresis, at present they seem to occupy a unique position among drugs with diuretic action

It is interesting that polysaccharide sulphates so different in source, composition, and molecular weight as heparin thrombocid, and Ro1-8307, should have diuretic actions of about the same magnitude and of exactly the same type. It is possible, too, that the dextran sulphate 'Dexulate' shares this diuretic action, since Jeavons et al in 1956 observed a patient with venous thrombosis associated with pulmonary embolism, who lost 8 5 kg in weight during the first 6 days of dexulate treatment Rapid disappearance of œdema in patients with thrombophlebitis during dexulate administration was also observed by Donzelot et al (1955)

Our own observations suggest that the natriuretic action of the heparinoid Ro1-8307 deserves further study, because this drug, in the dosage used, is almost devoid of anticoagulant action (Studer et al. 1956, Majoor et al 1960) Studer et al (1956) administered Ro1-8307 as a clearing agent to nineteen patients for 8 weeks, without toxic manifestations But their dose of 100 mg three times weekly was far lower than that needed for diuretic action.

In the short-term experiments we describe here, with daily doses up to 450 mg, the drug was tolerated without untoward effect by all patients except F—a girl with a nephrotic syndrome who vomited twice on the last day of drug administration With growing experience with the intravenous and intramuscular administration of Ro1-8307, both in our department and in the department of internal medicine in Amsterdam (Cejka et al 1960), vomiting and diarrhœa have been noted in only three other patients all of whom had membranous glomerulonephritis with severe albuminuria In two of these, who vomited [illegible] after their first dose of 100 mg intravenously, treatment was not continued In the third patient, who was in a remission after prednisone treatment, vomiting and diarrhœa started on the 9th day of therapy, when 400 mg. of the drug had been given intramuscularly Toxic manifestations subsided immediately when injections were stopped

These observations show that a careful watch for drug intolerance should be kept whenever long-term administration of Ro1-8307 in relatively large amounts is used for treating intractable retention of sodium and water.

Summary

The diuretic action of heparin was compared with that of the heparin congeners 'Thrombocid' and Ro1-8307. Each drug produced natriuresis and often slight potassium retention The renal excretion pattern following administration of these polysaccharide sulphates is very similar to that seen in Addison's disease or after administration of amphenone and spirolactones This points to their having an inhibitory influence on the secretion of aldosterone.

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Preliminary [illegible]

EFFECT OF [illegible] SPIROLACTONE [illegible] OF SODIUM [illegible]

Two types of drug [illegible] adrenal cortex [illegible] Heparin[1] and [illegible] secretion of aldosterone [illegible] block the effect of [illegible] substances by [illegible]

We have [illegible] separately and [illegible] sodium and [illegible] three patients.

Patient [illegible] Moreover, the patient [illegible]

[illegible] hypertension, was on a [illegible] constant, while the daily sodium output [illegible] from 98 to 10 mEq [illegible] 200 mg [illegible] immediately increased the [illegible] In the following week urinary [illegible] continued treatment [illegible] sodium excretion [illegible] metabolites [illegible] in the urine was impossible [illegible] determinations could be resumed, the aldosterone [illegible] was higher than before treatment Heparin [illegible] 200 mg. given intramuscularly twice daily [illegible] followed by a fall in aldosterone excretion [illegible] increase in urinary sodium output [illegible] hardly increased the sodium [illegible] of 0·5 g. chlorothiazide daily [illegible] was by this time in a state [illegible] sodium level having fallen [illegible]

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1. Majoor, C. L. H. [illegible] of the [illegible]
2. [illegible] Schlatmann, R. J. A. F. M. [illegible] vii, [illegible]
3. [illegible] ance in atypical
4. Cejka, V., de Vries [illegible]

Treatment with salt restriction and diuretics—of which mersalyl had most effect—resulted in a slow decrease of the central venous pressure, but this remained 2–4 cm above the normal level The œdema diminished as shown by the loss of body-weight After the loss of œdema she developed a voracious appetite and could hardly be satisfied with 1900 calories The intake of salt was 17 mEq per day In spite of treatment with 0 5 g chlorothiazide daily, no sodium was excreted in the urine Body-weight and central venous pressure gradually increased In this period the excretion of aldosterone in the urine was 40–60 µg per day (see fig 3) During intramuscular injection of Ro1-8307 (at first 100 mg and later 200 mg four times a day) the excretion of aldosterone decreased to 4 µg daily Sodium excretion increased On the thirteenth day of heparinoid treatment, while sodium excretion was on a level, SC-9420 (four doses of 200 mg) was given orally in addition This 800 mg prompted a massive excretion of sodium in the urine, continuing at least five days Central venous pressure and body-weight rapidly decreased. The sodium output exceeded and markedly outlasted that induced by mersalyl When the treatment with

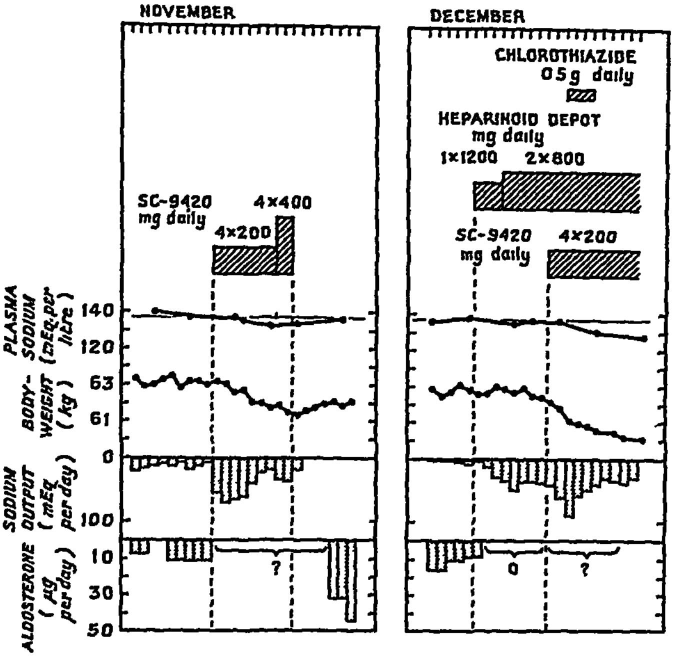

Fig 1 (patient 2)—Renal aldosterone and sodium excretion following treatment with spirolactone and heparinoid separately and simultaneously

PATIENT 3, a married woman born in 1902, has had congestive heart-failure since 1952

In 1955 she was operated upon for concretio pericardii (Professor Boerema, Amsterdam) after which kymography showed an increase in cardiac pulsations but the congestive heart-failure did not improve For four years she remained in fairly good condition She was on a salt-poor diet and received 2 ml mersalyl every fifth day, together with an adequate amount of ammonium chloride In spite of this regimen, in the spring of 1959, œdema increased and in August she was admitted to the Binnengasthuis The heart-failure was severe She had massive œdema and a very high central venous pressure, which amounted to 3 cm above the level of the sternal angle (see fig 2)

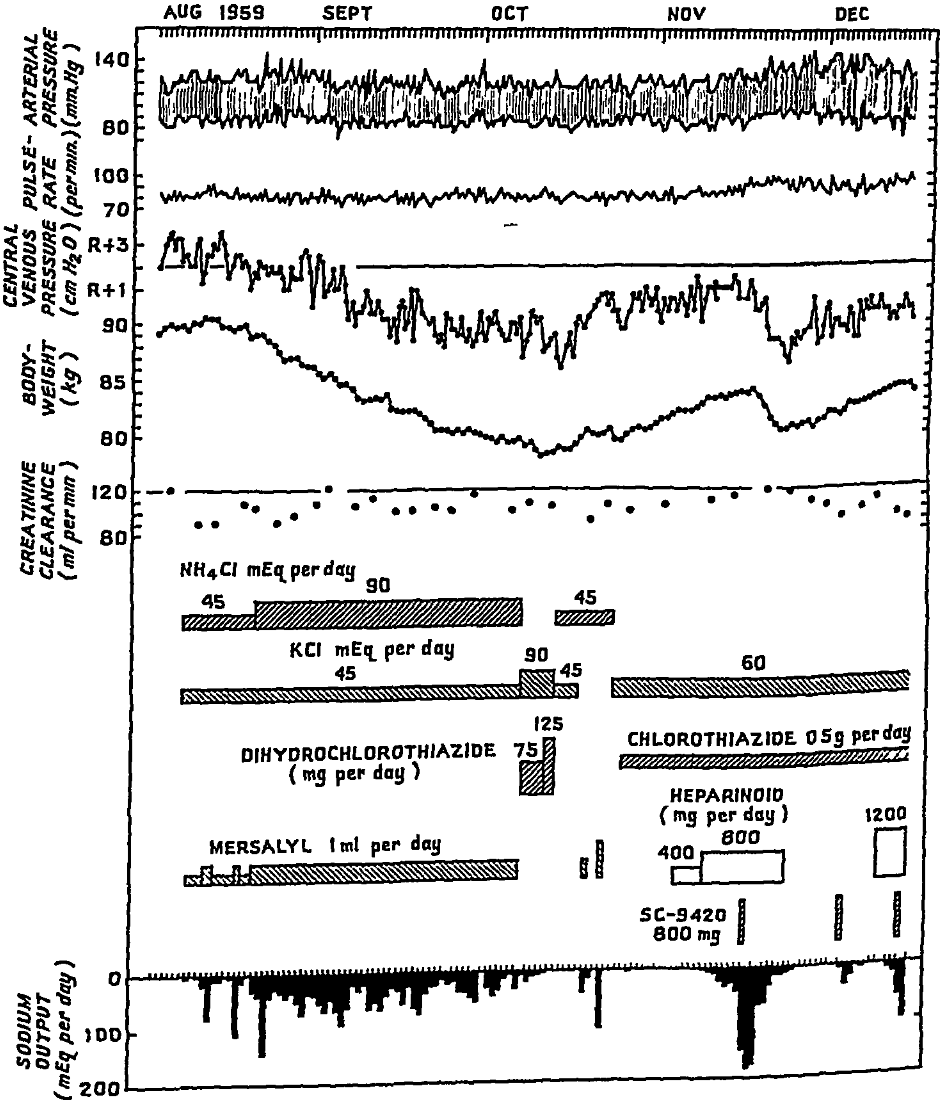

Fig 2 (patient 3)—Comparison of the natriuretic effect of mersalyl and the chlorothiazides with that of heparinoid and spirolactone administered separately and simultaneously The blood-sodium level (not presented) was almost constant

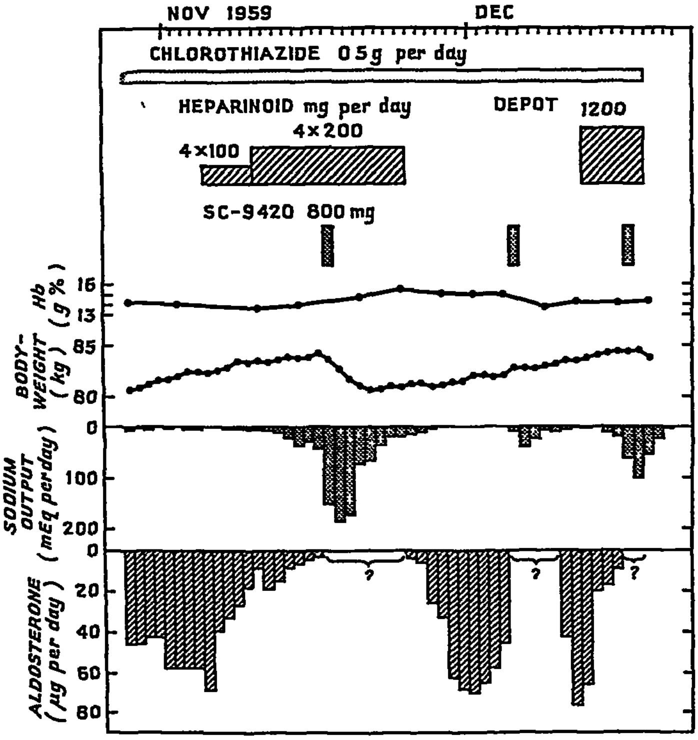

Fig 3 (patient 3)—Renal aldosterone and sodium excretion following treatment with spirolactone and heparinoid separately and simultaneously

heparinoids was discontinued, the excretion of aldosterone increased to control levels in four days Without heparinoid, administration of the same dose of spirolactone for one day resulted in a small excretion of sodium lasting four days Resumption of heparinoid administration, this time with 1200 mg of a depot preparation in one intramuscular injection daily, met with the same type of response Addition of 800 mg spirolactone again initiated a further appreciable rise in sodium excretion

The patient left hospital on Dec 18 in a good condition She continued collecting the twenty-four hours' urine That day and the two days thereafter she had no treatment The last dose of chlorothiazide was given on the 17th at 6 A.M Nonetheless the sodium output on Dec 18 was still high and then declined rapidly The blood-sodium level was almost constant during the whole period of observation, and the creatinine output in the urine fluctuated only insignificantly

In this case of secondary aldosteronism the effect of the combined treatment with SC-9420 and Ro1-8307 on sodium excretion is much greater than the sum of the effects of the two drugs separately Though the influence of aldosterone on tubular reabsorption of sodium must have been reduced to a very low level, the peak sodium excretion was much lower than that present in normal persons on a high sodium intake or in some patients with cardiac failure during a good response to digitalis Therefore we conclude that the sodium retention was caused partly by other factors of the same importance as aldosterone

The creatinine clearance was slightly higher during the period of greatest sodium excretion but stayed on the same level for some days, during which sodium was again retained. During the second sodium diuresis the clearance was on a lower level It is highly improbable that sodium excretion in this case was influenced by the alterations in the creatinine clearance

No side-effects of the heparinoid were noticed, coagulation-time was normal and signs of hæmorrhagic tendency were absent However, some of the patients with nephrotic œdema, who were treated with the heparinoid Ro1-8307 in the University Hospital at Nijmegen showed signs and symptoms that may be attributed to a toxic effect of the drug [2]

SUMMARY AND CONCLUSIONS

In three patients on restricted salt intake (two of whom had secondary aldosteronism) administration of heparin and heparinoid Ro1-8307 was followed by a gradual decrease in urinary aldosterone to levels found in normal subjects on an unrestricted salt intake Sodium output increased, the changes in sodium output not being related to changes in creatinine clearance

In a patient treated with 1200 mg heparinoid and 500 mg chlorothiazide daily, 800 mg of spirolactone given on one day increased the sodium output for five days, the effect being far more than additive The sodium output greatly surpassed that induced by mersalyl and the chlorothiazides in high dosage On the other hand, it was less than that seen in normal persons on a high sodium diet

Ro1-8307 was supplied by Hoffmann-La Roche Laboratories, Basle, and SC-9420 by G D Searle & Co, Chicago

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Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Evolution of Viruses

A MEETING was held in London on Jan 21

Prof C D DARLINGTON said that a change of host (as in myxomatosis when introduced into Australian rabbits, or measles when introduced into Polynesia) often means an increase of virulence—after which there is a sharp decline both in the virulence of the parasite and in the susceptibility of the host, apparently through natural selection. Transplantation by an arthropod vector can transform the character of a virus, and the question arises whether the vector finds the virus ready-made as an infectious organism. A nucleoprotein propagating itself normally in one organism may become a virus in another something transmitted by the cytoplasm in heredity, or generated by the cell, becomes communicable by infection On the other hand a virus can become a harmless nucleoprotein or become latent, doing no harm to its host. Latency is imagined to have existed in all situations where a new virus has arisen where no virus was known before

Mr P F MATTINGLY pointed out that though each virus is isolated in the tissues of the host, it has like other organisms an ecology of its own, independent of adventitious transfer to man or occurrence in atypical hosts or vectors At present the requirements for establishing a mosquito-borne virus are warm-blooded vertebrates, angiospermous plants, and blood-sucking mosquitoes The first two evolved together in the Tertiary period, and the viruses and mosquito vectors probably evolved with them. The fact that mammalian malaria parasites are transmitted by anophelines, and bird-malaria parasites (in the laboratory and therefore presumably in Nature) by culicines, suggests that anophelines evolved as mammal feeders and culicines (at least in part) as bird feeders The basic maintenance cycles of mosquito-borne viruses involve culicines only (except for the subgenus kerteszia), and this suggests that the primitive viruses of this group were bird viruses Aedes-borne viruses are confined to the tropics, culex-borne viruses are found in the subtropics, and tick-borne viruses in the northern steppes The explanation seems to be that aedes hibernate and æstivate in the egg, and culex hibernate and æstivate as adults, which permits them to withstand the severe conditions of the subtropics Further north, where only the resistant egg will serve for hibernation, aedes are the dominant mosquitoes, but they do not pass on the viruses through the egg, and are therefore unsuitable for maintaining them, and the mosquito-borne viruses are replaced by tick-borne viruses The West Nile virus is probably the most primitive of the group-B viruses and the picture would be of invasion from the subtropical savannah northwards to steppes and tick vectors, and southward tó tropical habitats and aedes vectors But possibly the Russian spring-summer viruses are the most primitive, and if this were so the picture might be simpler and more coherent

Dr C E Gordon Smith, taking up the evolution of arborvirus diseases, showed a list of the arborviruses known to cause diseases in man, but he noted that progress may occur from a virus infecting only an arthropod and transmitted through the egg, to a virus transmitted from arthropods to an animal other than man, thence by a second arthropod to man, and finally between man and man through this secondary vector Hence there may be many arborviruses still " in search of disease " The factors influencing the maintenance of arborviruses in Nature are extremely complex and are often strongly affected by human activity—e g, irrigation, insecticides, artificial immunisation, or the effect of sanitation on the age of the population The viruses themselves fall into several groups, but changes in virulence and antigenic structure, and phase variations, are all observed and are related to mutations Selection pressures occur in the vertebrate and arthropod hosts

Dr C H Andrewes remarked that the viruses are probably very old in evolutionary history, they probably evolved along with their hosts and vectors, and the tick-borne viruses may be the oldest Their evolution may be affected by short-term factors which are not very fundamental (as in influenza and myxomatosis) or by long-term factors such as those suggested by Mattingly

Prof D S Bertram referred to the fact that virus can pass more easily to the egg in ticks than in mosquitoes, having fewer membranes to cross in the process

Dr J S Porterfield suggested that there are two time-scales in the evolution of viruses, one of which is short-term and is being witnessed now, as in the development of the Chikungunya virus

Dr M G R Varma, who has worked on the Kyasanur Forest virus, pointed out that, experimentally, mosquito-borne viruses have been propagated in ticks, but not vice versa, which suggests that the tick-borne virus may be the more primitive Kyasanur virus is related to Russian spring-summer virus, but it is carried by hæmaphysalis and not by ixodes though these are abundant The Russian virus is transmitted by ixodes

Dr P B Stones observed that when mosquitoes first evolved there were no mammals, and if viruses then existed they must have been passed from mosquito to mosquito

Reviews of Books

Forensic Medicine

A Keith Mant, M D, lecturer, department of forensic medicine, Guy's Hospital, London London Lloyd-Luke Medical Books 1959 Pp 262 42*s*

Here is a well-written concise guide to the points which can be observed and the interpretations which may reasonably be made by general practitioners, police surgeons, and others called to see a body thought to be dead The book is intended also for those who may have to appraise injuries in the living or the dead, and for those asked to deal with an alleged sexual assault

When death is unexpected, it is very important that the initial examination of the body and its environment be conducted so that an opinion given at that time is well founded and not just a careless guess, otherwise, as Dr Mant points out, a family may suffer the early stages of an investigation of a supposed crime, later shown to be a natural death, or a murder may be unsuspected until after necropsy, by which time essential evidence may have been destroyed All that is described and well illustrated in this book is what may be seen by a careful observer, such as a general practitioner, no special forensic knowledge being required indeed, all specialised matters, such as necropsies, microscopy, and analyses, are excluded

What to do, and what not to do, when examining a supposedly dead body is followed by an account of up-to-date methods of estimating the time of death, the " virtual cooling time " method being explained in detail The characteristics of injuries, applicable to the living as well as the dead body, are dealt with at length, the examination of road accident victims being a useful feature Guns and gunshot injuries are carefully explained, and much attention is given to various causes of anoxæmia incidentally, perhaps the only illustration in the book to which exception might be taken is found at the beginning of the chapter on mechanical asphyxia Infant deaths, abortion, and poisoning conclude the first section of the book

The second part deals with the medicolegal aspects of sexual offences, and any doctor who proposes to examine the alleged victim or assailant in a supposed sexual assault would be well advised first to study this section in detail, for incomplete physical examinations and incautious opinions based more upon preconceived notions than on fact seriously endanger the liberty or reputation of one of the parties involved Dr Mant leaves the reader in no doubt as to the responsibilities of the examining doctor in such cases, but he also offers a comprehensive scheme for a proper examination

As is apt to happen in a first edition, there are a few trivial points which will doubtless be amended in subsequent editions (e g, in the legend to fig 82, reference should be made to fig 77), but they in no way diminish the considerable value of this realistic work which can be wholeheartedly recommended to all involved in medicolegal affairs At the very least, Dr Mant shows the doctor how to avoid the unhappy thought, " *What on earth am I supposed to see?* "

Antibiotic and Sulphonamide Treatment

A Short Guide for Practitioners A R Anscombe, M.S, F R C.S, D M Davies, D B Brown, M B, M M.S A, M R C O G, M.R C P Editor M E Florey, M D London Oxford University Press 1959 Pp 150 10*s* 6*d*

This little handbook is designed as a brief practical guide to the treatment of infections It outlines the principal features of the antibiotics and sulphonamides and gives clear instructions for their use and adequate warning about their toxic effects and dangers It is fully up to date and includes notes on several recently introduced antibiotics

There can be little doubt that the book well fulfils its limited purpose, and those who want for quick reference a short text dealing only with the practical aspects of these agents will find it an excellent choice

THE LANCET
LONDON 6 FEBRUARY 1960

The Sign of Babinski

Since **Babinski**[1] [2] described the extensor plantar response in man, it has been generally accepted as indicating a disturbance of function in the pyramidal tract **Walshe**[3] concluded that it was an integral part of the flexion reflex in man and was strictly homologous with the nociceptive flexion reflex in animals, described by **Sherrington**[4] It has long been known that a transient extensor plantar response may follow an epileptic fit and may appear in biochemical disturbances affecting the nervous system, such as hypoglycæmia, so it is clear that the presence of the sign does not necessarily indicate an anatomical lesion in the pyramidal system There has been some discussion and indeed criticism[5] [6] of the significance of the extensor plantar response as an indication of disturbed pyramidal function, and **Brain** and **Wilkinson**[7] have lately investigated the response in the human infant, using as stimuli pinprick and cold and, on the sole, key-drag

They studied 35 children, ranging in age from one day to twenty-seven months In children up to the age of eight days the responses obtained were almost always extensor and could often be elicited by pinprick or cold as high as the third thoracic segment, but the response was nearly always limited to the side stimulated The greatest activity of the extensor response was seen in children between five and twenty weeks old, being obtained as a bilateral response to all of the three forms of stimulus applied to the sole, and it could also be obtained bilaterally as a result of stimulating either thigh. Usually a bilateral response could also be obtained from the abdomen and upper chest, but it was definitely or doubtfully flexor almost as often as it was extensor from these levels

After the age of twenty-one weeks the receptive field shrank progressively from above downwards only 1 child over the age of twenty-three weeks gave any plantar response to a stimulus above the third thoracic segment, and after the age of nine months there was usually no response to stimulation of the thigh. The response to stimulation of the sole also altered in character, the extensor response became less definite or was replaced by a doubtful or a frank flexor, but, even during the second year of life, the response to a scratch on the sole was not always flexor—sometimes it was a weak flexor, sometimes a weak extensor, and sometimes even a definite extensor In general cold ceased to be an effective stimulus after the age of twenty-four weeks

Brain and **Wilkinson** think it probable that the conversion of the infantile extensor response to flexor and the progressive shrinkage of the receptive zone between the ninth and twenty-fourth months of life can be correlated with the progressive myelination of the pyramidal tracts during this period

Brain and **Wilkinson** also studied the plantar response in 31 children suffering from neurological disease dating from birth or very early in life, including cases of cerebral diplegia, and in 5 adult patients with virtually complete traumatic lesions of the spinal cord in the lower cervical region In the children cold was rarely effective as a stimulus A response to pinprick was evoked more easily the nearer the site of stimulus approached the sole, a response was obtained from the third thoracic level in only 4, from the abdomen in 13, from the thigh in 20, and from the sole in all 31 They conclude that the plantar responses of those children with congenital diplegia differ from those of normal infants in whom the pyramidal tracts have not become myelinated In particular the usual absence of a response to cold and the extent of the receptive field of the reflex correspond more closely to patients with spinal-cord lesions acquired later in life

Landau and **Clare**[8] examined the plantar response in 14 normal subjects and 12 patients with consistently extensor responses, using motion pictures and electromyographic recordings In the normal flexor response the usual pattern included strong contraction of the short hallux flexors, with an associated response in the dorsiflexors of the foot, the extensor hallucis longus was always electrically silent In the extensor response there was a tonic contraction of the short hallux flexors, contraction of the dorsiflexors of the foot and toes, and a strong contraction of extensor hallucis longus The essential phenomenon of the extensor reflex is therefore thought to be the recruitment of extensor hallucis longus into contraction alongside the other toe and foot dorsiflexors, with mechanical overpowering of the toe flexors In studying the changes in the response in several patients who had had acute spinal-cord lesions, **Landau** and **Clare** found electromyographic evidence of denervation in extensor hallucis longus and the dorsiflexors of the toes and ankles, and in 1 of these patients an extensor response became flexor in spite of evidence at operation of a virtually complete transection of the spinal cord They thought that the denervation of the anterior tibial muscles in these patients was due to a lesion of the external popliteal nerve from pressure In 1943 **Lewin**[9] also drew attention to the danger of pressure lesions of the external popliteal nerve in patients with spinal-cord injuries, although he did not study the effect on the plantar response

These observations of the effect on the plantar response of a peripheral nerve lesion in a patient with severe spinal-cord damage are important and may well explain some of the recorded cases in which the plantar response was flexor in the presence of known damage to the pyramidal tracts This is not, however, the only cause of flexor responses in spinal-cord lesions **Gordon Holmes**[10] in 1915, studying acute injuries of the spinal cord, recorded a flexion-adduction movement of the toes as the earliest reflex response after a severe cord lesion, this reflex might disappear after a few days and later an extensor response might be found This observation, confirmed by **Riddoch**,[11] is now well recognised and

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[1] Babinski J *C R Soc Biol*, *Paris*, 1896 3, 207
[2] Babinski J *Sem médicale*, 1898 18, 321
[3] Walshe F M R *Brain*, 1914, 37, 269
[4] Sherrington C S *J Physiol* 1910, 40, 28
[5] Lassek, A M The Pyramidal Tract its Status in Medicine Oxford 1954
[6] Nathan P W Smith M *J Neurol Neurosurg* 1955, 18, 250
[7] Brain, W R., Wilkinson, M *Brain*, 1959, 82, 297
[8] Landau W M, Clare M H *ibid* p 321
[9] Lewin, W *Lancet*, 1943, ii 756
[10] Holmes G *Brit med J* 1915 ii 769
[11] Riddoch, G *Brain*, 1917, 40, 264

usually indicates a poor prognosis for recovery of spinal-cord function. Brain and Wilkinson observe that in 1898 Sherrington had recorded a similar reflex in the monkey after transection of the cord below the level of the brachial enlargement, and that it has also been recorded in the baboon. It seems that when all other spinal-cord functions are abolished there is a rather feeble flexor reflex of the toes in response to a stimulus to the sole, which Gordon Holmes described as a "unisegmental reflex response in muscles supplied by the first sacral segment".

The Germ-free Animal

Pasteur was usually right, but his reasoned guess that mammalian life without bacteria is impossible was proved wrong even in his lifetime. The early attempts to raise germ-free animals were not very successful, but they failed not for lack of understanding of the problem but for minor technical reasons such as improper diets. Today rats, mice, guineapigs, rabbits, and chicks are all raised free from parasites of all sorts, within and without, as a routine procedure which has proved valuable in many kinds of research. Though this is not a cheap hobby for idle moments, the results seem to justify the trouble and expense. A monograph from the New York Academy of Science[1] gives a good idea of the techniques and the results to be expected and will encourage others to try the method.

On the same diets there is not much difference in the development of germ-free and conventional mammals. Analysis of the weights of individual organs shows that heart and brain are of the same size, but the germ-free animal has far less lymphoid tissue. If it is "infected" with a normal fæcal flora, the weight of lymphoid tissue soon reaches that of the conventional animal. If, on the other hand, the conventional animal is fed small regular doses of penicillin from birth, the weight of its lymphoid tissue is not much more than that of the germ-free stock. The development of the lymphoid tissue depends on the stimulus of the intestinal flora. In chicks—as the farmer knows—small doses of penicillin quicken growth, and it has been debated whether this quickening is due to an inhibitory action of the flora of the bowel on growth or to some stimulant action of the antibiotic. The germ-free chick grows at least as fast as the conventional bird fed with penicillin. Of the various species of bacteria in the chicken's bowel which have been fed singly to the germ-free chicks, only *Clostridium welchii* (type A) slows the growth-rate to "normal". Germ-free mice grow well on a diet lacking some aminoacids essential to the conventional mouse. If they are then given their normal intestinal flora they cease to grow: there is not enough of something for both host and parasite. Was the difference in size of adolescent boys in social classes I and V (which is no longer seen) attributable to some similar deficiency? So striking have been the facts elicited from these germ-free stocks that some biochemists are prepared to say that the science of dietetics must begin again from scratch.

The serum of germ-free mice contains an abnormally large amount of albumin (and for this there is no parallel) but only small amounts of gamma-globulin. It contains complement and properdin but no bacterial agglutinins unless the sterilised food contains dead bacteria. When exposed to an antigenic stimulus, the germ-free animal responds more slowly than the normal. The response to infections is curious and hard to understand. In the normal animal fed by mouth, *Shigella flexneri* is not easy to establish, but in the germ-free animal 9 or 10 organisms introduced by the same route will multiply to 10^9 within eighteen hours. Whereas these will produce no pathological changes, *Bacillus subtilis* causes a rapidly fatal disease, and the same is true of many other bacteria usually looked on as barely pathogenic. Clearly the germ-free animal offers an opportunity to investigate the nature of infections in cavities of the body which ordinarily carry a large mixed flora. We should be able to discover whether *Treponema vincenti* is the "cause" of an ulcerated mouth, or merely a normal inhabitant which takes advantage of existing disease to multiply exceedingly. Many species of bacteria have been blamed for dental decay: here is the possibility of examining their powers in isolation or in combination. Experiments with germ-free guineapigs have shown that, while *Entamœba histolytica* can survive and multiply in the bowel wall, ulceration does not begin until the normal bacterial flora of the bowel is introduced. On the other hand, the germ-free guineapig is susceptible to infection with species of worm whose natural hosts are the mouse or rat and which cannot be established in the normal guineapig.

Though the scope for inquiry is limitless, such research is by no means all easy going. For example, serum hepatitis can be established in one breed of germ-free chicks but not in another. The evidence of the part played by viruses in the production of spontaneous tumours breaks new ground but is hard to interpret. So far, moreover, few of the findings of this technique have had a practical application. The premature infant delivered by cæsarean section and kept in a sterile atmosphere might reach viable size a few days earlier. Almost the same benefit might be derived by feeding it small daily doses of penicillin, but he would be a bold pædiatrician who recommended this regimen. Experience has taught that minor infections do quite a lot to protect us against the major ones. If he was speaking of human life, Pasteur was after all nearer right than wrong.

The Role of the Stomach in Digestion

The stomach makes two contributions to digestion: it changes physically and chemically the food put into it, and it delivers its contents in a highly regulated manner to the duodenum. The processes of digestion within the stomach and the control of the secretions which contribute to them have been so intensively studied that the dependence of eupepsia on the proper control of gastric emptying tends to be overshadowed. Most medical students are made aware of Beaumont's *Experiments and Observations on the Gastric Juice and the Physiology of*

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[1] *Ann N Y Acad Sci* 1959, 78, 1.

Digestion (1833) and Pavlov's *Work of the Digestive Glands* (1916), but in fact digestion within the stomach is probably not essential for normal life It is usually accepted that the majority of patients with treated addisonian anæmia secrete neither acid [1] nor pepsin,[2] yet they are reported to be at least as healthy as patients of a comparable age [3] and not to be unduly susceptible to diarrhœa or dyspepsia [4] Although this view about the absence of pepsin in the gastric secretion of patients with addisonian anæmia is acceptable in a general way, some refined studies of gastric proteolytic enzymes by Taylor [5] have displayed new features which are too common to be called exceptional In an extension of earlier work [6] it has been clearly shown that gastric juice from normal persons gives two peak rates of digestion, one at pH 1 6–2 4 and one at pH 3 3–4 0 The activity at low pH is due to the classical pepsin,[7] but the cause of the second peak of activity at pH 3 3–4 0 is more controversial Taylor [8] measured the extent of digestion by the formol titration of carboxyl groups liberated from peptide bonds, and many of the digestion periods were long—three to six hours—by the standards of most other workers The measurement of carboxyl groups, which are produced in all stages of proteolysis, would be expected to give a different idea of digestion from that obtained by determining the rather special phenolic hydroxyl groups, as, for example, in the popular method of Anson and Mirsky [9] Under Taylor's conditions, with digestion periods usually of the order of three hours, as much as half the proteolysis by human gastric juice can be ascribed to a hitherto almost ignored enzyme acting at pH 3 3–4 0 Only 13 out of 23 patients with addisonian anæmia had even small amounts of proteolytic enzyme acting at pH 2 0, but 20 out of 23 had measurable activity between pH 2 6 and pH 5 0 [5] From further study it seems that in gastric juice from man there are two main pepsins—that is, proteolytic enzymes acting below pH 5 0 Moreover, one of these predominates in the pyloric mucosa and the other in the mucosa of the fundus and body of the stomach [10] The results of an examination of gastric secretion from patients with peptic ulcer [11] or addisonian anæmia [5] suggest to Taylor that in some circumstances the gastric mucosa may secrete abnormal pepsins

The main change of view resulting from Taylor's work is that proteolysis in the gastric contents is not dependent upon such high acidities as was previously thought As a consequence it now seems possible that gastric lipase [12] and salivary amylase, which have maximal activity at very low acidities, and gastric proteases, could all act more or less simultaneously in the same medium

Having considered what types of digestion could take place in the gastric contents it remains to discover to what extent food is digested before it is passed into the duodenum In view of the usual presence of acid and pepsin in the gastric contents it would be expected that the gastric digestion of protein would make a significant contribution to absorption In the studies of Maltby,[13] who gave 100 g of fried minced lean meat and 300 ml of water as a test-meal, the aspirated gastric contents contained as little as 25% unaltered protein when the pH was between 1 and 2 Even when the gastric contents were as weakly acid as pH 5 about a third of the protein was found to be partly digested, which gives in-vivo support to the views of Taylor on the other hand, in Maltby's investigations patients with addisonian anæmia accomplished very little or no digestion of meat. Although an exact comparison is impossible because of differences in chemical methods, it is interesting to compare the degree of digestion of meat under Maltby's conditions, which were particularly favourable, with that reported by Beazell [14] with normal meals which were recovered from the stomachs of 2 subjects who could vomit at will About 40% of the starch was digested in thirty minutes but practically none of the protein was completely digested Beazell also points out that much of the meal had left the stomach before digestion of protein had taken place

The idea that the stomach retains its contents until digestion is completed and only then transfers them to the duodenum should have begun to die with the appearance of Beaumont's monograph in 1833 and was convincingly refuted by McLure et al,[15] who showed that normal food began to leave the stomach within three to ten minutes of beginning a meal Nevertheless the concept of retention till digestion is completed is given in a current textbook Not only is gastric digestion of protein usually slow but much of the protein of a meal may have left the stomach before significant digestion could be achieved

Since the stomach has an incomplete action in digesting protein and begins to empty its contents into the duodenum very shortly after a meal is taken, it is reasonable to ask whether or not it makes any important contribution to digestive function Gastric emptying is not at all haphazard the rate of gastric emptying becomes slower as the concentration of nutritive material in the original meal is increased This regulation appears to be achieved via duodenal receptors which detect the products of hydrolysis of starch or protein, possibly by virtue of their osmotic pressure [16] There is the well-known slowing of gastric emptying in response to fat, which increases with the amount of fat in the meal [17] Gastric emptying is also adjusted in response to the initial volume of meals—for instance, the pattern of emptying with large meals is such as to give a sudden charge to the small intestine when the meal is eaten, followed by a slowly diminishing trickle of material which presumably matches the absorption[18]

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[1] Card, W I, Sircus, W *in* Modern Trends in Gastroenterology, 2nd series (edited by F Avery Jones) London 1958

[2] Ihre, B J E *Acta med scand* 1938, suppl 95

[3] Wilkinson, J F *Lancet*, 1949, i, 249

[4] Janowitz, H D Quoted in *Physiol Rev* 1959, 39, 492

[5] Taylor, W H *J clin Path* 1959, 12, 210

[6] Freudenberg, E *Enzymologia*, 1940, 8, 385

[7] Schwann, T *Arch Anat Physiol, Lpz* 1836, p 90

[8] Taylor, W H *Biochem J* 1959, 71, 73

[9] Anson, M L, Mirsky, A E *J gen Physiol* 1932, 16, 59

[10] Taylor, W H *Biochem J* 1959, 71, 384

[11] Taylor W H *J clin Path* 1959, 12, 338

[12] Schonheyder, F, Volquartz, K *Acta physiol scand* 1946, 11, 349

[13] Maltby, E J *J clin Invest* 1934, 13, 193

[14] Beazell, J M *Amer J Physiol* 1941, 132, 42

[15] McLure C W, Reynolds L, Schwartz, C O *Arch intern Med* 1920 26, 410

[16] Hunt, J N Macdonald, I, Spurrell W R *J Physiol* 1951, 115, 185

[17] Annegers, J H., Ivy, A C *Amer J Physiol* 1947, 150, 461

Nutritional disorders after total and partial gastrectomy are common,[19] and their study has made apparent the part which the stomach plays in digestive processes In particular the effect on the total digestive processes of bypassing the duodenum has become clearer The masterly study of LUNDH,[20] using new techniques with radio-tagged fat and protein and an inert marker, has shown that after Bilroth-II operations there is a notable failure of mixing of trypsin with the intestinal content, the absorption of protein in his patients being more abnormal than the absorption of fat After partial gastrectomy LUNDH found that the absorption of protein was correlated with the concentration of trypsin in the intestinal contents, whereas in normal persons these values were independent This finding was taken to indicate defective peptic digestion, thus putting the tryptic phase under strain The current interest in the digestion and absorption of protein in such patients is a fitting response to the emphasis laid by BRAIN and STAMMERS[19] on the need for studying nutrients other than fat in patients with metabolic difficulties after gastrectomy

There is a big functional reserve to the various components of the digestive tract, and, other things being normal, gastric digestion *is* dispensable, but the gastric reservoir function is important for the proper time relationships between presenting material to the intestine and evoking the secretions of the pancreas Moreover, various subjective disturbances are common after gastrectomy, apparently as a result of too rapid filling of the intestine[21]

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[18] Hunt, J N, Macdonald, I *J Physiol* 1954, 126, 459
[19] Brain, R H F, Stammers, F A R *Lancet*, i, 1951, 1137
[20] Lundh, G *Acta chir scand* 1958, suppl 231
[21] LeQuesne, L P, Hobsley, M, Hand, B H *Brit med J* 1960, i, 141

Annotations

MIRAGE OF HEALTH

WE are all specialists now, and it is notorious that a surgeon on biochemistry and a biochemist on surgery are equally likely to talk rubbish Such trespasses in other demesnes are not however always disastrous and can be most illuminating Dr Rene Dubos is one of the most distinguished of living bacteriologists and his essay, *Mirage of Health*,[1] ranges almost every field of medicine and far beyond The basis of his argument is that the formula

Host + specific parasite = specific disease

is seldom if ever true Somewhere on the left side of the equation are other factors, some of which we know so well that we tend to forget them and others which in our ignorance we have barely recognised Because perhaps Pasteur's *Memoire sur la fermentation* was contemporary with talk about "the struggle for existence", our profession has tended to treat all bacteria as enemies the only good microbe is a dead microbe If the slogan "Kill that germ" was applied conscientiously we would not only lack cheese and beer but most of us would die either of a deficiency of vitamins or by infection by organisms with which we now live in happy symbiosis There are, in fact, few bacteria which cannot survive in the human body without harm to either party bacterial disease is an upset of this mutual tolerance by the missing factors in the equation Even in such infections as gonorrhœa where these factors seem of small account a perfect prophylactic and treatment has not extinguished the disease For this we need an understanding of social habits which we have not got

History suggests that the most venomous epidemics are those imported into a society where the "causative" organism has been hitherto unknown Measles reduced the population of Fiji by one-quarter in one year (It is a curious fact that the import of diseases from the temperate zone into the virgin populations of the tropics has done far more damage than the reverse traffic Have our institutes of tropical medicine been looking in the wrong direction?) The lethal consequences of these introductions have been shortlived, and quite quickly adaptations in the host (and perhaps the parasite) make the disease no more deadly than it was in its original home At this moment the phenomenon is exemplified by myxomatosis in the rabbit The infectious diseases which plague us day in day out seldom come in epidemics but are the result of minor changes in the internal and external environments—fatigue, diabetes, perhaps worry—which supply the missing factors in the equation The deaths in concentration camps were due to our common diseases occurring more frequently and with greater virulence Our ecological balance is indeed precarious and (which is more important) always changing So long as the changes come slowly we can usually adapt ourselves to them individually and as a race Disaster is the consequence of great changes made too abruptly the sedentary man running for a train or the prize cattle breathing London smog One of the great difficulties of planning for health (or for war or even holidays) is that experience is of limited value We can do no more than guess the dangers ahead and our surmises are not always correct

Every civilisation has cherished a dream of perfect health and happiness, usually in the dim past or far far away Today we tend to look forward "Health is purchasable", and we see all round us new projects, new committees, and new buildings We owe much to the laboratory but perhaps not so much as we think The changes in environmental hygiene which freed us from typhoid and typhus—clean food, clean water, clean air—were devised and implemented by men who had never heard of bacteria Antibiotics have reduced mortality but may have added to morbidity By design the experimentalist limits the conditions of his inquiry to obtain a clear and certain answer The manifold factors which decide the larger issues of health and disease in ourselves, our homes, our community, and our nation are too complex as yet for comparable analysis Are our criteria of health beyond criticism? The legend of the "bonny baby" was exploded years ago and survives only at rural baby shows Those who talk comfortably of "the conquest of disease" should remember that at 45 our expectation of life is not much better than that of our grandsires every year we find it necessary to spend more and more on health (and in the U S A, Dr Dubos says, this amounts to 10% of personal income) and at least one in ten of us will spend some days, weeks, or months in a mental hospital

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[1] Mirage of Health Utopias, Progress and Biological Change By RENÉ DUBOS London Allen & Unwin 1960 Pp 221 21s

On and around these matters Dr Dubos has written an exceptional book—plain, lucid, elegant, and lively It draws its facts and illustrations not only from the corpus of medicine but from authors from Lao-tzu to Proust. It is logical and persuasive rather than dogmatic It is in fact a confession of faith and humility by a great scientist. We commonly hear the complaint that the young doctor of today knows more and more about less and less Reading Dr Dubos' book will make him a more useful member of our profession than an exact memory of the seventeen causes of enlargement of the spleen—and in this respect we are all young doctors

PERTHES' DISEASE

Perthes' disease is now one of the commonest disorders of the hip in childhood It affects children mainly between the ages of 3 and 8, and the symptoms are often trifling There is occasional pain in the leg, a limp which may be difficult to detect, and some limitation of abduction and internal rotation The radiographs may remain normal for some months after the onset of symptoms, but, when changes do appear, the head and neck of the femur undergo a slow process of disorganisation and reformation over a period of two, three, or more years

O'Garra [1] distinguishes two types of radiological changes in the femoral head, depending on whether the whole of the head is affected, or only the anterior half or two-thirds, and suggests that the prognosis is more favourable with incomplete involvement. Of much greater importance is the age of onset and the sex of the patient. Using the final shape of the head as an index of resolution—and there is little else one can rely on in the child—there can be no doubt that girls do less well than boys On similar criteria the younger the age of onset the better the prognosis Until these two factors have been considered in O'Garra's figures, it is hard to tell whether partial head necrosis carries a better prognosis than complete necrosis, although the assumption seems reasonable

No general agreement has been reached upon the pathogenesis of Perthes' disease The radiological changes suggest an initial necrosis of bone, followed by reconstruction Histological studies [2] of biopsy material from 23 hips confirm that necrosis affects the marrow, cartilage, and bone of the femoral head Ponseti [3] suggests that these changes are secondary to disruption of the epiphyseal cartilage plate, and are due to a disturbance of the blood-supply as the retinacular vessels cross the disrupted epiphyseal plate That the lesion is one of avascular necrosis was first proposed by Legg [4] and is still the most commonly accepted view Cavanaugh et al [5] suggested that osteochondritis of the femoral head is associated with a high incidence of colloid goitre in the families of affected patients, but Beiler and Love [6] were unable to find evidence of hypothyroidism in a group of patients with Perthes' disease Similar radiological changes, however, may be present in the cretin and the mongol, and in the reticuloses and certain other general affections of the skeleton In these conditions progressive destruction and replacement of the femoral head is absent

Most patients with Perthes' disease are treated by some method which attempts to relieve weightbearing in the leg In some centres rest in bed with traction is considered essential until the head begins to reform Other surgeons suggest that a weight-relieving calliper is adequate, and Evans and Lloyd Roberts [7] believe that recumbency has no advantage over an ambulant method of treatment. Many would agree with Legg [8] that relief from weightbearing in no way affects the end-result Before committing these children to a period of institutional treatment which may well last a year or more, two things must be established firstly, that the prognosis of the untreated disease is sufficiently grave to justify this line of treatment, and secondly that prolonged treatment in recumbency improves the prognosis Of the long-term effects of Perthes' disease little is known Ratliff [9] has shown that, although radiological changes may persist in the hip into early adult life, function is rarely affected at this age If, as seems likely, osteoarthritis is an uncommon sequel there can be little justification for long-term orthopædic treatment in childhood

PROGNOSIS IN GENITOURINARY TUBERCULOSIS

THE place of combined chemotherapy in the treatment of urogenital tuberculosis is now so secure that it is hard to recollect the former ravages of the disease and to appreciate what has been accomplished Barely twelve years have passed since the introduction of streptomycin (followed shortly afterwards by *p*-aminosalicylic acid and later by isoniazid), and a sufficient interval has only just elapsed to allow a full appraisal of its effect on what is often a chronic disease. In this respect the report of Gale and Kerr [10] from the Toronto Hospital for Tuberculosis is of outstanding importance, not only for its large number of treated cases but for the almost similar number of earlier cases which serve as a control Historically Toronto has a special interest in the disease since it was here in 1929 that Harris [11] did his classical work on the association between renal and orthopædic tuberculosis Some of his original patients are now included in a group of 82 cases followed for upwards of thirty-five years, and they represent an era when neither nephrectomy nor chemotherapy was in use. These cases give a remarkable picture of what used to be the natural history of tuberculosis, with a mortality-rate of 40% within five years and an eventual survival of 32% (described as " good chronics ") in which something approaching symbiosis was fortuitously achieved between host and invader

It might be assumed that with the subsequent vogue for nephrectomy in unilateral disease these morbidity statistics would improve, but in a further series of 347 consecutive cases treated where indicated by nephrectomy there was little apparent change. 43% died within five years, although 48% were still surviving over a period extending up to fifteen years By contrast, however, the addition of chemotherapy—and in particular triple-drug therapy—is shown to be outstandingly effective In a third series of 389 cases treated by a combination of nephrectomy (where indicated) and chemotherapy, followed for a period of up to ten years, the mortality-rate fell to 4% Of the last 214 consecutive patients in this series receiving six or more months of chemotherapy none died from renal tuberculosis Whereas this phenomenal improvement is undoubtedly largely due to sustained triple-drug therapy, Gale and Kerr also acknowledge the ancillary benefit of certain conservative and reconstructive surgical procedures thereby made possible They rightly claim, however, that progress in the management of genitourinary tuberculosis during the past ten years ranks paramount among all the remarkable advances in urology within this period

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[1] O'Garra, J A *J Bone Jt Surg* 1959, 41B, 465
[2] Haythorn, S R. *ibid* 1949, 31, 599
[3] Ponseti I V *ibid* 1956 38A 71
[4] Legg, A T *Boston med surg J* 1910, 162, 202
[5] Cavanaugh, L. A , Shelton E K., Sutherland, R. *J Bone Jt Surg* 1936, 18, 957
[6] Beiler D D , Love W H. *ibid* 1956 38A, 320
[7] Evans, D L., Lloyd Roberts, G C. *ibid* 1957, 39B, 782
[8] Legg A T *ibid* 1927, 9, 26
[9] Ratliff, A H C. *ibid* 1956 38B, 498
[10] Gale, G L., Kerr, W K. *Canad med Ass J* 1959, 81, 977
[11] Harris, R I *Brit J Surg* 1929, 16, 464

TEMPERATURE REGULATION DURING FEVER

THOUGH fever is a very common accompaniment of disease or tissue damage, elevation of body temperature does not in itself clearly benefit the patient, except perhaps in a few special situations For this reason fever is sometimes regarded as a manifestation of failure of the normal controlling system, but this is far from the truth For many years there has been evidence suggesting that the body temperature is controlled at a higher level in disease.

The concept of fever as a change in the setting of a central thermostatic mechanism was first formulated by Von Liebermeister,[1] and subsequent work by Stern[2] substantiated this hypothesis Stern observed the development of sweating or of shivering in patients with and without fevers, when they were warmed or cooled by gradually changing the temperature of a bath in which they sat He found that the change in rectal temperature when patients began to sweat or to shiver was the same in the pyrexial and apyrexial groups Subsequent experimental work in man has in general confirmed these findings Park and Palmes[3] found that the injection of bacterial pyrogens into normal subjects produced the same elevation of temperature in warm or cold environments All these findings suggest active regulation of body temperature during fever, though the evidence is not entirely conclusive

Further convincing evidence of active temperature control has been described by MacPherson[4] In a long series of experiments he obtained very complete records of the responses of three normal subjects to standard exercise during environmental heat stress During these experiments one subject developed a febrile illness characterised by cough and malaise, his temperature was raised by 0 5–1 5°F for six days During this time the subject was able and willing to continue with the experiment, thereby providing very interesting information

Before the onset of fever this subject responded to exercise with an increase of rectal temperature which was almost identical with that of his companions During the fever this pattern was exactly reproduced, at a higher level The absolute temperature increment due to exercise remained the same During exercise at moderate environmental temperatures the normal subjects showed a fall of skin temperature, with recovery during the subsequent rest period This pattern was also reproduced by the febrile subject, at a higher absolute temperature level During exercise this subject's sweat-rate did not differ significantly from that of his companions

These experiments confirm and extend the previous findings, suggesting that the febrile patient responds to various thermal stimuli in much the same way as the normal subject, but at a higher level of temperature It is difficult to avoid the conclusion that his temperature is regulated in the same way If the regulating mechanism is normally active, the temperature rise in fever must be actively produced Why this happens is unknown

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[1] Von Liebermeister, C Handbuch der Pathologie und Therapie des Fiebers Leipzig 1875

[2] Stern, R *Z klin Med* 1892, 20, 63

[3] Park, C R , Palmes, E D Medical Department Field Research Laboratory, project no 6-64-12-06 Fort Knox Ky, 1948

[4] MacPherson, R. K *Clin Sci* 1959, 18, 281

B P C 1959

THE new edition[1] of the *British Pharmaceutical Codex* is dated 1959—a vintage year for official publications on prescribing costs—and against this background the *B P C* assumes great importance The conscientious and selective use of the *Codex* by medical students and doctors would encourage the critical attitude and keener appreciation of the place of pharmacy in relation to therapeutics that can lead to prescribing which is both sound and economical

It is strange that the *British Pharmacopœia* (published under the ægis of the General Medical Council) continues to be a book of reference used almost exclusively by pharmacists, while the *Codex* (published by the Pharmaceutical Society of Great Britain) has become one of the most important books available to doctors The subject matter of the two is, of course, much the same, but there are striking differences in presentation Thus, the *Codex* includes paragraphs on the actions and uses of drugs these are not intended to convert it into a textbook of pharmacology, but they are invaluable in presenting concise information about the effects of drugs and the relative merits of their various preparations Thus, the *Codex* is a book of capital importance as an ancillary to standard works on therapeutics

Although drugs, or particular preparations of drugs, which have been deleted from the *Pharmacopœia* are likely to disappear also from the *Codex*, it is the traditional policy of the *Codex* Revision Committee to retain many of these preparations, if they are widely used, and look at them occasionally during a further period of five years There is clearly a place for this conservative attitude, for although the factual data of the *Pharmacopœia* and *Codex* inevitably have much in common, the books are in many ways complementary Allowance must also be made for doctors who are not prepared to modify their prescribing habits simply because, for various reasons, certain pharmaceutical preparations are no longer " official "

The additions to the new *Codex* include 70 new general monographs, and 20 of these refer to drugs already included in the *B P* 1958 Among the monographs which deal with the more specialised materials (biological products, surgical ligatures, and sutures), poliomyelitis vaccine and rabies antiserum deserve mention The Formulary (part VI of the *Codex*)—perhaps the most valuable section for the prescriber—contains some 79 new items, but 44 of them represent " salvage " from those deleted from the *B P* There are long lists of deletions under monographs and under formulary Some 26 preparations suffer total eclipse, in that they no longer appear in either the *B P* 1958 or the *Codex* 1959 But few doctors will feel their withers wrung by the demise of infusion of quassia, solution of mercuric chloride, and the dilute solution of ammonium acetate The rise and fall of cream of penicillin (also among the 26 condemned to the twilight of obscurity) may, however, cause some to reflect on the transient glories of therapeutic fame

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[1] British Pharmaceutical Codex 1959 7th ed *Council of the Pharmaceutical Society of Great Britain* London Pharmaceutical Press 1959 Pp 1301 *70s* The *Codex* comes into force in the United Kingdom on July 1, 1960

Public Health

EFFICACY OF AN ANTI-SMOKING CAMPAIGN

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THE scientific status of health education is not impressively high. Though more and more importance is attached to it as a function of the public-health services, there has been a notable shortage in this country both of theoretical analyses of the assumptions upon which health education is based and of evaluative studies of specific campaigns Intention and effect have too often been confused, and the success of a programme has been measured by the enthusiasm with which it was planned and executed.

If educational measures are to be the principal means of trying to reduce current levels of tobacco consumption, assessment of their value is as important as assessment of the value of more conventional prophylactic procedures Some local health authorities have already responded to the recommendation of the Ministry of Health and the Department of Health for Scotland that they should bring home to the public the health hazards associated with cigarette smoking, and many more may be planning to do so The experience of the Edinburgh Health Department, which carried out a fairly extensive anti-smoking campaign and asked the University Department of Public Health and Social Medicine to evaluate its efforts, may therefore be of some interest.

The Campaign

The budget for the campaign totalled £4350—corresponding to about 2½*d* per head of population—although certain additional money was available in the ordinary course of health education expenditure The campaign was developed on the following lines

Press—Paid display-advertising material in which the Medical Officer of Health warned the public of the danger of cigarette smoking was accepted by all newspapers with a wide local circulation. Each of the three Edinburgh newspapers also gave the campaign powerful editorial support and provided much space in its news columns, gossip column, sports page, and photographic sections Support from the national Press was considerable though less extensive.

Posters—About 120 16-sheet posters were displayed on hoardings throughout the city, and about 3000 double-crown and crown posters were displayed in factories, offices, clubs, clinics, consulting-rooms, libraries, public baths, and shops. A poster was also shown in all the buses in Edinburgh.

Leaflets and letters—30,000 copies of the British Medical Association's booklet *Smoking—the Facts* were distributed at meetings and to schoolchildren. A special Edinburgh campaign leaflet was designed by one of Britain's foremost display artists, and 150,000 copies were distributed through a variety of channels A clear and forceful letter from the Medical Officer of Health was sent to every household in Edinburgh.

Meetings—24 meetings were held at which over 2600 teachers heard the case against smoking presented by a doctor using visual aids in the form of a specially prepared flannelgraph and the B B C.'s film *Facts and Figures—Smoking and Lung Cancer* Every class of secondary-school children was visited by a medical member of the Health Department. Meetings were arranged with almost all the parent-teacher groups in Edinburgh, at which the film *1 in 20,000* was shown. About 70 public meetings were held in different parts of the city in cooperation with various associations, clubs, &c.

Other media included a rally of voluntary workers, a concert for young people, a Sunday cinema meeting, and radio and television publicity

The Evaluation

Two parallel samples of the adult population of the city were drawn, one sample to be interviewed before the opening of the campaign, in November, 1958, and the other to be interviewed six months later The object was to discover any shift in the distribution of smoking habits and/or of associated beliefs

The methods of sampling and interviewing have been described by Cartwright, Martin, and Thomson (1959a) 590 interviews were completed before the campaign and 596 after it these correspond to response-rates of 85% after removal from the initial samples of those who had died or left their original address between the compilation of the electoral register and the survey period.

Smoking Habits

There was no indication that the campaign persuaded people to give up smoking Similar proportions of people in the two surveys said that they smoked regularly—that is, at least one cigarette a day—and there was no significant change in the proportion who claimed to have given up smoking *

The forms of tobacco consumption also remained unaltered, the ratio of pipe to cigarette smokers was similar on the two inquiries and there was no evidence that filter-tipped cigarettes or cigars had increased in popularity

These negative findings are confirmed by the replies given to a direct question included in the second inquiry Not one of our informants claimed to have given up smoking, even temporarily, as a result of the campaign, although, curiously enough, as many as 12% of all the people interviewed claimed to know someone who had stopped smoking because of the campaign. On the other hand, 9% of the smokers thought that their smoking habits had been influenced by the campaign; the majority of these claimed that they had been persuaded to smoke fewer cigarettes Similarly, when the members of our samples were asked whether they were smoking more, less, or the same amount as six months previously, a comparison of pre-campaign and post-campaign replies suggested that a higher proportion of those interviewed in May, 1959, were under the impression that they had reduced their tobacco consumption. But when we compared the actual levels of tobacco consumption reported before and after the campaign we found no significant difference. It is very possible that the campaign succeeded in persuading a number of people to try to smoke less, and that in retrospect they may have felt their attempt to have been more successful than it was

Beliefs about the Health Hazards of Smoking

Our November inquiry had shown that all but 2% of the adult population had already heard of the postulated connection between lung cancer and smoking although many of them regarded the theory with varying degrees of scepticism. Hence there was virtually no scope for raising the level of public awareness of the hypothesis, and indeed after the campaign the proportion who maintained that they had not heard of it was still about the same.

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* Copies of statistical tables which give the findings in detail may be had from the authors

On the other hand, there was a considerable opportunity to convince people that the hypothesis is correct Yet after the campaign the proportion prepared to accept it was found not to have risen significantly ($P > 0\ 05$) In spite then of the repeated warnings of the Medical Officer of Health almost as many people were still unwilling to believe that lung cancer is more likely in smokers than in non-smokers

In the first (pre-campaign) inquiry people were rather more ready to attribute such ill effects as coughs, breathlessness, bronchitis, and catarrh to smoking than they were to admit that it could cause cancer As these conditions were not mentioned in the campaign publicity, it was perhaps surprising to find a significant rise in the proportion who thought smokers more liable to breathlessness, bronchitis, coughs, catarrh, or heart-disease than non-smokers, although there was no change in the proportion who thought smokers more liable to indigestion, rheumatism, stomach ulcer, or tuberculosis

Similarly, although the campaign did not increase the proportion of smokers who supposed that smoking had affected their own health, it did produce a notable increase —from one in five to one in three—in the number who believed that their health might be adversely affected in the future This change was brought about by more smokers specifying breathlessness and cough as possible future effects, the proportion mentioning cancer as a personal risk did not rise significantly

This greater readiness to accept smoking as a possible cause of conditions which are more common and for the most part more trivial than lung cancer was wholly unexpected Two causal processes appear to be involved

The first of these could be a form of emotional blockage The widespread fear of cancer—long nurtured by a conspiracy of silence—generates a resistance that factual assertions do not easily overcome This resistance is strengthened by the feeling of guilt which may be aroused by incrimination of a habit which the individual knows that he ought to be able to control

The second process is one of deflection and dilution the charge against smoking is translated into terms which are more familiar and more acceptable Before the campaign there had been no great reluctance to concede that smoking might be harmful to health, and afterwards there was an even more widespread readiness to recognise its hazards But they are hazards more commonplace than lung cancer and on the whole far less frightening This latter tendency has affinities with the process of explaining the ætiology of major diseases in terms of simple everyday hazards, which we have called " reduction to the familiar " (Cartwright and Martin 1958, Cartwright, Martin and Thomson 1958)

The anti-smoking campaign, then, apparently heightened public awareness of some of the possible effects of smoking upon health, but did not increase acceptance of the idea that cigarette smoking may cause lung cancer

General Attitudes to Smoking

One of the more hopeful findings of the pre-campaign inquiry was that just over two-fifths of current smokers said that they would like to give up smoking if they could do so easily This proportion had not increased after the campaign, nor had there been any change in the pattern of reasons put forward for wishing to give up smoking Before and after, expense was most commonly cited, fear of cancer was mentioned by only 2–3% of smokers, and other health reasons were given by about one smoker in seven

Some change was evident, however, in attitudes towards smoking in young people Whereas before the campaign slightly under two-thirds of our informants felt it was " wrong " for young people to start smoking, by May this proportion had risen to just over seven-tenths Similarly, after the campaign, parents with children above the age of 15 were more inclined either to regret that their children smoked or to rejoice that they did not

Beliefs as to the advantages of smoking also seemed to have been modified slightly There was a little more scepticism about the view that smoking helps people to relax, 11% rejecting it compared with only 6% six months earlier Nevertheless it was still accepted by four-fifths of the post-campaign sample, while a similar proportion thought that a cigarette helps to relieve nervousness or embarrassment This latter fraction had not changed during the campaign

In general, then, there does appear to have been a very modest change in public attitudes There is certainly nothing to suggest that smoking was becoming socially unacceptable, but there was probably a slightly wider acceptance of the idea that one ought not to encourage young people to start it

Perception and Recall of the Campaign

To discover the extent of public awareness of the campaign, our post-campaign sample were first asked whether they had heard, seen, or read anything in the past few months about smoking and lung cancer Nearly three-quarters said that they had

Newspaper articles were recalled more often than any other form of publicity They were mentioned spontaneously by just over half our informants, compared with slightly more than a quarter who mentioned posters Other forms of publicity, such as leaflets and radio and television programmes, were recalled spontaneously by less than a tenth However, the proportions who claimed to have noticed the various publicity media rose appreciably when specific questions were asked Newspaper publicity was recollected by a further 20% (so that altogether nearly three-quarters of our sample claimed to have noticed this) and two-thirds had seen posters The posters displayed on buses seem to have had substantially more impact than those on the hoardings Meetings and film shows had been attended by only 2% and 3% respectively Only 15% reported having seen a leaflet on smoking and lung cancer, though the Public Health Department had circulated 150,000 copies—one for every three persons in the city Similarly, rather less than a third said that their household had received a letter from the Medical Officer of Health, although such a letter was supposed to have been sent to every householder in Edinburgh

After asking questions about the specific aspects of the campaign, our interviewers said, " These things were, in fact, all part of a campaign about the connection between lung cancer and cigarette smoking Did you know there had been a campaign ?" Replies show that a fifth of the adults in our sample had been unaware of it

Men were rather more likely than women to know about the campaign More of them had read about it in the newspapers and seen the posters on the buses and on the hoardings There was no difference between the sexes in the proportion who had seen any films or leaflets, attended meetings, or received a letter from the Medical Officer of Health

The campaign also had rather more impact on younger than on older people The proportions who were aware of the campaign or who had seen the posters or who had seen a leaflet were significantly lower among people aged 55 or more In contrast, the proportion who had read anything in the newspapers did not fall off to any appreciable extent with increasing age

The group of semi-skilled and unskilled workers and their wives was rather less aware of the campaign than those in skilled manual work, while the most widespread awareness was found among professional and blackcoated workers and their wives A similar trend was also shown for certain specific aspects of the campaign—newspaper publicity and letters from the Medical Officer of Health, but posters in buses were less often noticed by the middle-class members of our sample

These factors—sex, social class, and to a lesser extent age—are all associated with differences in smoking habits (Cartwright, Martin, and Thomson 1959a), the category of smokers, compared with that of non-smokers, contains higher ratios of men to women, of younger to older women, of unskilled to skilled manual workers, and of manual to blackcoated workers It is not surprising, therefore, to find that the impact of the campaign varies as between groups classified according to smoking habits The small numbers involved make cross-analyses difficult to interpret, but they seem to suggest that the variations may be explained largely in terms of the different sex, age, and social class characteristics of smokers and non-smokers respectively

Compared with people who were non-smokers or occasional smokers or people who had given up smoking, smokers were more inclined to say they had noticed something about the connection between lung cancer and smoking in the last few months On the other hand, they were less likely to have attended any meetings or to have noticed the letter which was sent to householders by the Medical Officer of Health There was no significant difference between smokers, non-smokers, and others in the proportion who had read anything in the newspapers or noticed the posters on the hoardings, but among the non-smokers a smaller proportion had seen the posters in buses or were aware that there had been a campaign.

Discussion

Although the anti-smoking campaign reached a large majority of the city's adult population through one medium or another, its coverage by no means equalled that achieved in the mass-radiography campaign a year before The latter, though concentrated into a much shorter period, had an impact upon almost the entire community (Cartwright, Martin, and Thomson 1959b) Newspaper and poster publicity in the mass-radiography campaign was seen and recalled by 95% and 91% of the population respectively, compared with 73% and 64% in the anti-smoking campaign.

If it was ever expected to have an immediate and appreciable effect upon smoking habits, then the anti-smoking campaign must be deemed a failure, since our surveys showed no statistically significant shift in the distribution of these habits after the campaign Failure in this sense might have been predicted from the outset, for our pre-campaign inquiry had shown that, although 98 adults in every 100 had heard of the possible association between lung cancer and smoking, the number who had therefore given up smoking was very very small

Nor can the campaign be judged successful in having persuaded people that smoking does in fact increase the risk of lung cancer Unexpectedly, it increased the proportion of people who thought smoking harmful to health in other ways, but there was no parallel increase even in the proportion of smokers who would like to give up smoking if they could do so easily One cannot, of course, assume that a sustained campaign might not have a cumulative effect, the hardening of attitudes towards smoking among young people provides a hopeful indication, albeit on a modest scale. Nor may it be taken for granted that a campaign whose focus was directly upon either the minor health hazards or the expense of smoking might not have more rapid and significant effects

It is arguable that educational campaigns of this nature are based upon unrealistic assumptions about perception and motivation. But, although their chances of bringing about direct and immediate changes are extremely slender, they may in the long run help to change the climate of opinion in such a way that young people become less likely to start smoking Against this, the difficulty which habitual smokers experience in giving up the practice makes it improbable that large-scale changes can be accomplished until ways can be found of assisting the many people who would like to stop smoking but cannot do so by their own unaided efforts

Summary

A health education campaign in which the Edinburgh Public Health Department tried to bring home to the public the risks of lung cancer associated with cigarette smoking was evaluated by the Edinburgh University Department of Public Health and Social Medicine. The evaluation was based upon interviews with random samples of the adult population of the city—590 before the campaign and 596 six months later

The campaign did not increase the proportion of non-smokers in the population, and the ratio of heavy to light smokers remained unchanged Nor was there any significant increase in the proportion who believed that smoking may cause cancer of the lung There was, however, a rise in the proportion who thought that smoking could be harmful to health in other ways—e.g , in causing cough—though these had not been mentioned in the campaign

No change was evident in the nature and extent of smokers' ambitions to alter their own habits, but a greater proportion of those interviewed thought it undesirable that young people should start smoking

About three in four of our informants reported having been aware of the campaign, newspaper articles and posters were the only publicity media frequently mentioned. Awareness of the campaign as a whole and of specific forms of publicity were found to vary with age, sex, and occupational class

Campaigns of this type are unlikely to produce changes in behaviour except possibly in an indirect and long-term fashion

This inquiry was supported by grants from the Chest and Heart Association (formerly the National Association for the Prevention of Tuberculosis) and from the British Empire Cancer Campaign We should also like to acknowledge the help and encouragement of Prof J H F Brotherston, Prof John Crofton, and Dr H E Seiler, and the valuable assistance of Miss Alice Stephen.

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Extension of Poliomyelitis Vaccination

The Minister of Health announced on Monday that the age limit for free poliomyelitis vaccination is being raised to cover all persons who at the time of their application for vaccination are under 40 The following small groups will also be offered vaccination

(*a*) Persons going to visit or reside in a country outside Europe, other than Canada or the United States of America.

(*b*) Practising dental surgeons, dental students, dental hygienists, student hygienists, dental surgeons' chairside assistants, and their families

(*c*) Practising nurses not working in hospitals (those working in hospital are already eligible) and their families

(*d*) Public-health staff who might come into contact with poliomyelitis cases, and their families.

In a letter to local health authorities the Minister says these extensions are based on the advice of the Joint Committee on Poliomyelitis Vaccine At the same time the committee recommend that efforts should continue to be directed to the vaccination of as many as possible in the existing priority groups "Thus, although the acceptance rate among children born since 1943 is generally high, special efforts are still required in those areas where the rate is below the national average, and the need for raising the rate among expectant mothers continues in most areas Authorities have, with the co-operation of general practitioners, and by hard work and imaginative publicity measures, to a large degree surmounted the difficulties encountered in obtaining a satisfactory response from the group born between 1933 and 1942" Executive councils are also sending a letter to all family doctors about the extension of the programme

By the end of last year registrations for vaccination passed the 13 million mark. Nearly all of those registered had had at least two doses of vaccine and over 7 3 million had received three In the 16–26 age-group, a total of about 2 7 million, or 46% of those eligible, had registered, and almost all had had at least two injections For children (1943–59 age-group) the acceptance rate rose to 75 4%, and 9 5 million had received two or more doses

The provisional number of cases of paralytic poliomyelitis last year fell below 1000 for the first time for 13 years the total was 914 The provisional number of both paralytic and non-paralytic cases was 1345, which was also the lowest since 1947 It compared with 2370 in 1958 The previous lowest total was 2177 in 1948 The highest number of cases notified in any one week during 1959 was 58 for the week ended Aug 22 The lowest figure was two cases during the week ended Dec 26 This is the lowest number for any week since the last week in 1946 when only one case was notified

1959

Provisional figures for England and Wales in 1959 were published on Jan 23 by the Registrar General in his weekly return

The number of *live births* was 750,170—i e., 16 5 per 1000 population, which is the highest rate since 1949 *Infant mortality* was 22 0 per 1000 live births (22 6 in 1958, 23 1 in 1957, 23 7 in 1956, and 32 4 in 1949) The death-rate was 11 6 per 1000 population (11 7 in 1958 and 11 5 in 1957) The *excess of births over deaths* registered in 1959 was 222,596, the biggest since 1948, when it was 307,072 15,009 *stillbirths* were registered in the year, giving a rate of 20 7 per 1000 live and still births (21 6 in 1958 and 22 5 in 1957)

Health Statistics for Scotland

The Department of Health for Scotland has published the first[1] of a new series of annual reports giving detailed statistics about health and health services in Scotland It deals with 1958 and gives more detailed figures over a wider range than have so far appeared in Scotland in a single volume

Until 1958, the annual reports of the Department of Health included statistical information about health services It was decided that the ordinary departmental report for 1958 (already published) should include only limited statistical material, and that a separate more detailed volume of health statistics should be published It includes population and other vital statistics and figures showing causes of death and illness in Scotland in 1958 Under some heads it covers a number of years before 1958 In the section on the hospital and specialist services, comprehensive figures are given showing the number of beds used for various types of illness in the regions, and the number of staff of different types employed in the hospitals There are also sections on the maternity services, infant and child health, and general medical, dental, and ophthalmic services Another section gives figures showing the cost of the health service under various heads

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[1] Department of Health for Scotland Scottish Health Statistics 1958 H M Stationery Office Pp 205 12*s* 6*d*

Conference

RADIATION PROTECTION AND MARROW TRANSPLANTATION

At a conference held at the Oak Ridge National Laboratory, Tennessee, on Jan 8–9, progress in protection against radiation was reported by various groups in the United States

D G Doherty (Oak Ridge) said that no recently synthesised compounds tested had been superior to aminoethyl isothiourea (A E T), for which maximum protective effect in mice gave an LD_{50} of 1100–1200r D P Jacobus (Walter Reed) had obtained good results with mercapto propyl- and ethyl-amines, and with 5-hydroxytryptamine there was significant protection in mice and rats, but not in dogs, apart from slight delay in fall of white-blood counts J Maisin (Armed Forces Institute) had used tritium-labelled A E T to determine its distribution in the mouse after intraperitoneal injection. Autoradiographs appeared to show widespread uptake in liver, spleen, brain, kidney, lung, and pancreas, and also in spontaneous tumours such as ovarian adenocarcinoma, hepatoma, angiosarcoma, and reticulosarcoma, but it was not clear whether the material was intracellular or not.

Other workers in the Armed Forces Institute had shown marked protective synergism in mice, using A E T and 5-hydroxytryptamine At 2500r there was only a 25% mortality V di Stafano (Rochester) had found A.E T to have acetylcholine-like effects on the gut, which were blocked by atropine both in vivo and in vitro

A E T had been used clinically by J V Schlosser (New Orleans) in more patients There was no evidence of tumour protection, but so far there were too few controls to assess the degree of protection of the patient M Kelly (National Cancer Institute) presented good evidence from controlled experiments in dogs that A.E T did not protect tumours, but did protect the animals against radiation. J A Cohen (Netherlands) reported that the effect of A E.T on thymocyte protection in vitro correlated inversely with oxygen consumption and suggested that A E T exerted its effect in vivo in this way

BONE-MARROW TRANSPLANTATION

N Gengozian (Oak Ridge) reported his findings of differences in the antigen recognition mechanisms in mice, using red cells of different species Sublethal irradiation lengthened the induction period following red-cell injection. The more closely related the donor species, the greater the lengthening Young mice had longer induction periods than older mice and gave lower antibody titres For effective heterologous marrow transplants in irradiated mice, larger quantities of cells were needed for the rabbit than the rat, the hamster being intermediate W Dameshek (Boston) had shown inhibition of antibody formation to soluble antigens by rabbits treated with 6-mercaptopurine in doses of 3–6 mg per kg Such failure of response persisted for about six months, as judged by response to further challenges with the same antigen, but there was no failure of immunisation to other soluble antigens However, such prevention of acquired immunity could not be demonstrated with skin grafts, though with big doses of 6-mercaptopurine some delay of graft rejection was demonstrable E Simmons (University of Chicago) reported similar experimental results in rabbits using sublethal irradiation instead of 6-mercaptopurine

J W Goodman (Oak Ridge) had shown that when isologous heparinised whole blood was injected into irradiated mice, together with homologous marrow, there was an increased mortality, which did not occur if the blood was irradiated with 75r first In discussion many made the point that lymphocytes were possibly responsible G Popp (Oak Ridge) had shown graded survival of irradiated mice given different amounts of parental marrow, and on the basis of these results suggested that in human subjects too few marrow cells were being given. On a weight-for-weight basis a 70 kg man should receive about 1 05 × 10^{11} cells—far more than is being given at present. Dr Cohen showed that the interval between sublethal irradiation and time of injection of heterologous bone-marrow was extremely important in determining survival and incidence of secondary disease. If bone-marrow transfusion was delayed until twenty-four hours after irradiation, survival was much increased. The possibility was raised that some cells responsible for "recognition" might persist in the host for some hours after irradiation.

J ANDERSON (Texas) reported rapid hæmatological recovery in monkeys given 2.5–3.5×10^{12} bone-marrow cells (isologous) three days after irradiation with 900r.

Dr SIMMONS and others agreed that the chances of treating systemic tumours successfully by irradiation were poor at present. In rats and mice sterilisation of solid tumours and leukæmic tissue required about 4000r, whereas the present sublethal working limit, except possibly in animals treated with A.E.T. and 5-hydroxytryptamine, was about 1500r, using A.E.T. or marrow transfusion alone. There was still a wide gap to be spanned.

Medicine and the Law

Drink and Diminished Responsibility

DESCRIBED by the prison doctor as a psychopathic personality, a 19-year-old soldier has been found not guilty of murder on the ground of diminished responsibility. He was convicted of manslaughter under the Homicide Act 1957, and sentenced to life imprisonment.

The prisoner was charged with the murder in December, 1958, of a woman whose mutilated body was found in bed. The murder remained unsolved until last November when the police took his fingerprints in connection with another charge. After his arrest, the prisoner made a statement in which he described how he killed the woman; he also referred to attacks on two other women.

Dr Francis Brisby, principal medical officer at Brixton prison, said that, in his view, the prisoner had a psychopathic personality, which expressed itself in aggressiveness without sufficient cause and in criminal acts which induced no remorse or shame. When he was 15 his headmaster had described him as difficult and precocious. Two years ago he had tried to hang himself. For a year he had been drinking heavily. He had claimed that he never committed any offence except when in drink. The encephalograph findings were abnormal.

Similar evidence was given by Dr Denis Leigh.

Summing up, Mr Justice Donovan said that if the jury accepted the evidence that the prisoner was suffering from an abnormality of the mind which substantially impaired his responsibility for the killing, they should find him guilty of manslaughter instead of murder. In his statement to the police, the prisoner had said: "It is when I get drinking I do these things. I am all right when I am sober." If a normal person got drunk or drank to excess and in that condition killed another, it would be no defence to say that he lost his self-control or that his self-control was diminished. The section in the Homicide Act dealing with diminished responsibility was not intended to be, nor was it, a charter for drunkards.

His Lordship continued that two doctors had expressed the view that even if the prisoner did not drink he would still suffer from an abnormality of the mind which substantially impaired his responsibility. "You are not bound by what the doctors have said. If you prefer to accept what the man himself has said, on the grounds that probably he knows best, you are entitled to do on that basis and say guilty of murder."

After the jury had brought in a verdict of manslaughter, his Lordship said that it would be unsafe to impose a sentence of a fixed term of years at the end of which the prisoner would be set free even if he were as dangerous as he was now. The sentence must be one which would enable the authorities to detain him until they were satisfied that he could safely mingle with his fellow creatures once again.

It has for many years been a principle of English law that loss of self-control through drunkenness is not a defence to a criminal charge. The summing-up in this case indicates that there has been no change in this principle as a result of the passing of the Homicide Act. The defence of diminished responsibility under that Act requires some abnormality of mind, and Mr Justice Donovan was surely right to tell the jury that mere drunkenness did not suffice.

Medical Education

THE NEW AFRICAN SCHOOL

THE Nuffield Foundation has offered £250,000 to the University College of Rhodesia and Nyasaland towards the establishment of a medical school at Salisbury on the lines recommended by the Rhodesia Medical School Planning Committee. This committee[1] has produced two reports, the first[2] of which proposed that a medical school should be part of the University College while the second[3] outlined a curriculum which has attracted much attention and was republished at some length in our columns.[4]

The grant is offered on the understanding that the teaching hospital takes the form of a new multiracial hospital on the University College campus. The planning committee's design for the medical course calls for more integration than is usual between the preclinical and the clinical parts of the course, and by putting the various departments in close proximity the University College has an opportunity to create a medical school which might become a model.

When the new medical school is established, it will initially be an affiliated institution of the University of Birmingham. The planning committee thought that the school should provide its successful students with a qualification which would be widely accepted, rather than with a diploma of only local value. The University of Birmingham agreed to help over this, and the details of its relationship with the African college are now being worked out.

While this relationship continues, students of the new medical school will be admitted to medical degrees of the University of Birmingham, and appointments to the staff of the medical school will be made only in agreement with the university. For its part, the university will ensure that the shaping of the curriculum to meet local needs and opportunities does not affect the standard of the course or of the examinations required. The relationship between the university and the university college will continue until the reputation of the new medical school is so securely established that local degrees which will be widely accepted can be awarded. If thought desirable, the association of the two schools may indeed continue in some form after the university college has become a full university awarding its own degrees in faculties other than medicine.

It is expected that very close personal relations will develop between the medical school at Salisbury and the medical school and the teaching hospital in Birmingham. Staff will be exchanged and joint research undertaken. It is being suggested, for example, that all members of the staff of the medical school at Salisbury should also be supernumerary members of the staff of the appropriate department in the Birmingham medical school. When first appointed, they would spend a period teaching at Birmingham, and at intervals thereafter they would revisit Birmingham to engage, perhaps for a term, in teaching, research, and other departmental duties.

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[1] The chairman is Mr Leslie Farrer-Brown and the members Prof Melville Arnott, Prof T H Davey, Prof A D M Greenfield, Prof P B Medawar, Dr Honor Smith, Prof R Milnes Walker, and Miss Grace McDonald (secretary).

[2] *Cent Afr J Med* June, 1958.

[3] *ibid* March, 1959.

[4] *Lancet*, 1959, i, 929.

In England Now

A Running Commentary by Peripatetic Correspondents

AIR travel is a chancy business at this season. At Rome airport we were told that the plane for Vienna might not be able to leave that night, because of fog at the other end Until the weather, or the situation, became clearer, would we mind waiting? Dinner perhaps, at the company's expense? Inconvenience much regretted Finally we boarded the Viscount about 7 30 P.M There were only 2 of us, and I suggested to my companion that with the two charming, and unemployed, air hostesses we might try to make up a bridge four, but the unenterprising fellow preferred to sleep We were making, not for Vienna, but for Stuttgart, where we picked up 16 stranded passengers from London Vienna still being fog-bound, the plane's destination was to be Graz, and there, sure enough, we were decanted into a bus and conveyed to the station, where the airline representative dipped into his pocket and bought 18 first-class tickets to Vienna At 1 15 A M., now a rather morose band, we boarded the Balkan express, which fumbled over the 200 kilometres to the capital with no great zeal Between snatches of sleep I listened to another of the 18 grumbling at the slowness of the train and the woes of all rail travel But as, at 5 45 A M, we crept out into the murky capital, I reflected that we should be heartily thankful for this old-world way which was there to serve us when the modern-wonder way had failed

* * *

I was frightfully excited by the figures A rough count showed a tremendous difference between the results for the patients who were getting my cherished new treatment and for the control group Of course, I knew it clinically But how splendid to prove it by statistics

I have lately taken a course in statistics, so I knew what to do I borrowed a calculating-machine for the weekend and roped in my wife—first to keep the children quiet, and then to work the machine for me She grumbled occasionally and the children grumbled a lot The cakes burned in the oven and the Sunday joint never got cooked at all It was an unsatisfactory weekend from the point of view of human relationships and bodily comfort But I didn't mind I was much too busy covering sheet after sheet with my calculations

At least, I didn't mind until Sunday night. Then I minded a lot My results weren't statistically significant. I just couldn't believe it The whole world seemed to crash about my ears Then my wife made some coffee and reminded me soothingly that statistics never proved anything I recovered sufficiently to write my paper I became almost pompous about it "Of course", I wrote with aplomb, "the fact that these results are not statistically significant only confirms our view that it is clinical judgment that counts, and in no way invalidates our findings"

Tomorrow I'll return that damned calculating-machine to its owner and never borrow it again In future I'm going to trust to clinical judgment during the week and enjoy my weekends

* * *

Copying case-histories for the files of the medical school is always somewhat of a problem, for the handwriting of house-physicians needs extensive study and a prolonged acquaintance with medical terms Each new typist endows us with a series of usually infuriating approximations, but our latest indomitable novitiate, who refused to be beaten by any scribble, commands our respectful admiration One of her typescripts runs

"*Has been feeling* '*dizzy*' with his hypolemine drug recently No pselpilatiars No spirein Very shallow complexion *Moderately* dyspureic with slight cyarosis A/B Standing V space 5" fism *midline* No mgms CHF =JVP=O" *H/S* Triple rdtchin Vesic breathing aneas V/F nasal and equal parthride Few asal eceptitatioss Cheek urine *Alhunan + + Eurio NAD*

4 5 57 Mouth and throath sowing evidence of incease inflamation reddened day coaked

5 5 57 *Has developed R parohibis* for pencillen and ghrephohugum

9 5 57 Parabibs inversing Pyrenial Breathing with markde unspiratory thoidor Indrowinging of chest Acccuory unocles of perpüatior archive Chonic trüchihings of arms and head Rehanded on submit"

Examples of her work are unhappily limited, for we felt it would be a pity to spoil her natural talent by an unduly prolonged acquaintance with medical literature.

* * *

I do not mind being called a stuffed shirt Television-soaked teenagers can keep their gibes and their jargon. I belong to a different world of visual stimuli, old-fashioned, solid, three-dimensional, flickerless, and mercifully silent Tucked away behind the stairs is the little room I call my study, with a book-case full of faded medical textbooks and holiday brochures of places we could never afford to go to A pleasant place for dreams and daydreams, away from the record-player, the radio, and the telly an English oasis in the yackering desert of show business If the stuffed shirt fits, I am proud to wear it but I will not stand for any aspersions on my other stuffed and stuffy friends A tiptop collection they are, too all round my study wall The pike from the edge of the reeds by the island that was a bitterly cold day for spinning, and Jock Thompson knew how to trade on vanity when he charged me a deal too much for stuffing the thing The otter pad from that morning when I fell in. The hare pad which was all that was left by the time we plodded up the hill on New Year's Day The snarling fox mask over the door he was the one that murdered a couple of dozen of our pullets one October night, and paid for them next day Then there is the smiling fox by the fireplace. A friendly chap I think I shall have all my fox masks mounted with their mouths shut in future They look much more foxy and Corgi-like much more ready to join in forty winks by the fire Solid, silent, long-standing friends

So I was pained to see an exhortation in the agony column of my favourite newspaper to get rid of the rubbish in our attics to some covetous box-number who wants to buy stuffed fish, animal heads, and similar trophies Just like that it seems so soulless Can it be that some pools-winner is trying to purchase the priceless heritage of the still waters above our weir, some forecaster to cast his sordid golden lure towards my pike, some eight-draws expert to draw my coverts, to bid his twenty-four against my foxes' points, to back his form against my hare's? And then to have the unpardonable nerve to call them rubbish And insinuate that I entertain my friends in the attic

When the time comes for the last tidy-up of my study I shall command my executors to stuff the lot of us all in one box.

* * *

Village shopkeeper "We're out of friars' balsam, but my daughter always rubs 'Vick' on Johnny's chest when he's poorly you did say it was for Carol, didn't you?"

Puzzled farmer's wife "No, I said it was for our cow"

* * *

On reading the Registrar General's Statistical Review Part II Tables, Civil

In England, Nineteen Fifty Seven,
Many a good soul went to Heaven—
Many a woman, many a maid,
Many a man in many a trade,
And as for the income of them as passed over
Why some was in poverty, some was in clover

There was some died o' drinkin' and others o' boxin'
And some hadn't taken their tet antitoxin,
There was some died o' workin' and some had a trauma
(Although thanks to the Union I ain't feared of the former)
And a few had a sickness and some had a tumour
But a terrible lot o' them died of ill-humour

In England, Nineteen Fifty Seven,
Many a good soul went to Heaven—
Many a Mister, many a Miss
Departed to eternal bliss,
But as to their religious sect,
It didn't make much odds, I expect.

Letters to the Editor

TREATMENT OF INGUINAL HERNIÆ

SIR,—As operations for hernia are about the commonest of all, we must commend the surgeons of St. Thomas's Hospital and the investigators, Mr Shuttleworth and Mr Davies, for showing in your issue of Jan. 16 that there is still no cause for complacency in the treatment of inguinal hernia. Few of those who embarked on the primary repairs of the 204 indirect and 94 direct hernias would have believed that 1 in 7 and 1 in 6 respectively would recur

One of the more solemn thoughts in connection with operations for hernia is that recurrences of even the third and fourth generation can be permanently repaired by a well-planned soundly executed operation, and all must agree with the authors that it is "difficult to escape the conclusion that the remarkable results obtained on recurrent herniæ are partly related to the extra care that is called forth by these herniæ" Doubtless the more experienced operators would also be called forth for the recurrent herniæ, and though we are all capable of making a botch of things from time to time, care, knowledge, and experience evidently help So much for the human factors

It seems that the method may also be a help, and Mr Shuttleworth and Mr Davies give general commendation to the nylon darn technique, for the 18 recurrent herniæ repaired by this method with no recurrence seem to be top of the bill, and results with nylon darns appear to be unbettered for those primary repairs more extensively used. Has nylon any special properties to commend it in addition to it being easy to insert? I believe it has, for when it is used as a thick single strand it retains tensile strength even after long periods of implantation in the tissues Linen, silk, and cotton sutures and also braided nylon, floss nylon, and any preparation of nylon in the form of fine weave all have their tensile strength reduced to nil after six months in the tissues But the thick no 7 single strand of nylon retains at least two-thirds (and probably more) of its tensile strength after eleven years in situ, and though the tissues do have some effect upon all implanted nylon the thickness of the strand is sufficient to stand up to the weakening influence of the body's chemicals Thick strands darned into a mesh and lying in the fibrous tissue formed in and around a darn continue to act as part of the buttress and are especially protective during high strains The evidence in support of these facts has been submitted elsewhere for publication and calls for no elaboration here.

Those who may wish to try nylon as a darn in the inguinal canal should not be put off by talk of sinuses When nylon is used in closing incisions higher up in the abdomen after operations on the alimentary tract, sinuses undoubtedly occur at times, but the incidence of sinuses arising from nylon buried in the depths of the inguinal canal, even in patients with strangulation, is extremely low, and is far outweighed by the advantages Almost all sinuses after infection or hæmatoma will close if the infection is treated by antibiotic and the sinus by patience Catgut does well in closing the external oblique, leaving the area pliant and the darn impalpable

The Radcliffe Infirmary,
Oxford
G E MOLONEY

ESTIMATION OF BLOOD-ALCOHOL BY BREATH ANALYSIS

SIR,—I am a little perturbed by the rumour that the 'Breathalyzer' is to be used as a means of estimating blood-alcohol In fact, it measures the amount of alcohol in an aliquot of expired gas It is probable that in a healthy resting subject the vapour pressure of alcohol present in his alveolar gas will be in equilibrium with that in the arterial blood. For many years now it has been realised that a sample of this gas may be obtained only from trained healthy subjects, such a sample cannot be obtained from untrained subjects whose lungs are at all emphysematous Moreover, the alcohol concentration in the expired gas of a given subject will depend critically on the rate of pulmonary ventilation, it should be easy for a partially intoxicated subject to hyperventilate for a minute or two before giving the required sample and thus halve the concentration of alcohol in his lungs The relation between the alcohol in expired gas and in the tissues, although explicable, is not at all simple I foresee many a happy hour spent in court by medical experts reconciling the results given by the breathalyzer with the facts of a case as presented by the prosecution or defence

Institute of Diseases of the Chest,
London, S W 1
F J PRIME.

PULMONARY DIFFUSING CAPACITY

SIR,—The single-breath method of measuring the pulmonary diffusing capacity for carbon monoxide which has been modified and developed by Forster et al [1,2] has not fared well in your recent issues Firstly, Professor Melville Arnott (Jan. 2) refers to Bates and Christie [3] who did not use the test and, secondly, Dr Jones and Mr Meade (Jan 9) have set about improving the test on an erroneous assumption. The improvement depends on the recalculation of the breath-holding time to allow for the time taken to deliver the alveolar sample, and the assumption is that this is important because the alveolar sample is large and consists of several litres

The misunderstanding has undoubtedly arisen from the description of the method by Ogilvie, Forster, and others,[2] who state that all the expirate is collected after the first litre, which is rejected because it is contaminated with dead-space gas However, it is quite clear from their later discussion about different portions of expired alveolar gas, that only a small sample is required for gas analysis (approximately 300 ml.) and that this is taken from the second litre From personal experience of making many measurements with Forster, I can state that in practice the collecting period is always kept as short as possible

It is doubtful if it is necessary to adopt the modified method for measuring the "effective" time of breath-holding except in patients suffering from severe impairment of the expiratory flow rate Since the problem then is to get a sample large enough for gas analysis, because of air trapping due to forced expiration, the error arising from large changes in alveolar volume during expiration, which is also mentioned by Jones and Meade, becomes unimportant.

Department of Pharmacology
and Therapeutics,
Queen's College, Dundee.
R. S MCNEILL

SIR,—Dr Jones and Mr Meade have put forward an ingenious and convincing explanation for the fall in pulmonary diffusing capacity which has been observed during breath-holding [1,2]

It seems that this fall is an artefact and can be abolished by timing the breath-holding periods from the start of inspiration to the midpoint in time (instead of the start) of sample collection, and then subtracting $^{3}/_{10}$ of the inspiratory time. It is questionable, however, whether the errors which they seek to overcome are either consistent or great enough to justify adopting their more complicated methods of timing and collection for routine clinical purposes

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[1] Forster, R E., Fowler, W S, Bates, D V, Van Lingen, B *J clin Invest* 1954 33, 1135
[2] Ogilvie, C M, Forster, R. E., Blakemore, W S, Morton, J W *ibid* 1957, 36, 1
[3] Bates, D V, Christie, R. V *Clin Sci* 1950, 9, 17

My colleagues and I[2] were able to collect adequate samples from each of our 28 untrained subjects in from 1 to 2 seconds. In this group, Jones and Meade's timing corrections would have produced variations of about 5% in calculated diffusing capacity. Providing that the subject is told to expire with all his might, he will add little to the sample after 2 or 3 seconds, although, in emphysematous patients especially, a noisy expiratory effort may continue for several seconds more. When sample collection is continued beyond this initial period of 2 or 3 seconds, an error is more likely to arise if, as suggested by Jones and Meade, a fixed proportion of the total collection time is counted as time available for diffusion. On the other hand, when the sample is collected within 2 or 3 seconds, these timing corrections seem scarcely worth while.

I do not think therefore that the proposed modifications to the breath-holding test are necessary for ordinary clinical purposes, but I would like to congratulate Dr. Jones and Mr. Meade on their solution to a problem which has mystified workers in this field for a number of years.

Liverpool Stanley Hospital,
Stanley Road, Liverpool

COLIN OGILVIE

C-REACTIVE PROTEIN IN BURNS

SIR,—Your stimulating leading article of Jan. 16 on the still very obscure and controversial subject of toxæmia of burns encourages me to recount some interesting observations which have been made on patients from our burns unit.

It occurred to us that it would be worth studying the behaviour of C-reactive protein (C.R.P.) in the blood of patients with burns, in the hope that serial quantitative estimations may provide a useful guide in the assessment and prognosis. With this object in view a new technique for the qualitative and quantitative estimation of C.R.P. has been developed in our laboratory. It is based on immunodiffusion on cellulose acetate and permits the test to be performed on serum or on whole blood from a finger prick, thus enabling frequent serial estimations to be carried out even on children and severely burnt patients.

We have carried out a series of investigations on patients with burns of widely different area, depth, and clinical severity. In about 40 cases so far investigated we have found that the presence and the level of C.R.P. in the blood appears to be closely correlated to the extent, depth, and severity of the burns. Curves obtained from several estimations of C.R.P. follow quite closely the progress of tissue breakdown and also the clinical state of the patient.

A certain minimal amount of tissue damage has to be present before the C.R.P. can be detected. With the same surface area involved, full skin loss produces a much higher level of C.R.P. than a superficial burn. In other words, the greater the tissue damage the higher the C.R.P. level. The presence of C.R.P. is detected within 24 hours from the time of the burn, sometimes even within 12–16 hours. In moderately severe, uncomplicated cases progressing towards recovery the C.R.P. level rises steadily and reaches a peak in about 5–7 days. With uneventful recovery and satisfactory healing, the C.R.P. level drops steadily until no more C.R.P. can be detected. In milder cases the increase of the C.R.P. level may last only a few days.

Complications involving further tissue necrosis, or acute inflammation with infection, may cause a secondary rise in the C.R.P. level, which may precede overt clinical manifestations, and thus indicate some unsuspected tissue damage. In severe cases the C.R.P. level rises steeply until a high titre is reached. Recovery is accompanied by a steady fall of the C.R.P. level. In fatal cases an abrupt drop was sometimes observed in the terminal stage. This drop may coincide with the hypothermic phase. In very severe burns, particularly in old patients, the rise in the C.R.P. level may not be dramatic and will reach only a comparatively low level. This might conceivably be associated with an overwhelming metabolic failure or, if death occurs in the first few days, the peak values may not have been reached.

The results so far obtained indicate that the estimations of C.R.P. *may be of considerable value in the* assessment of the severity of burns, and of the efficacy of therapeutic measures (be they conservative or surgical), and may also be of some help in the prognosis. The subject is now being investigated in detail, more material is being collected, and after a significant number of cases have been investigated it is intended to publish a full report.

Queen Mary's Hospital
Roehampton, London, S.W.15

J. KOHN

WITHHOLDING OF SICKNESS BENEFIT

SIR,—It was interesting to read that another medical man (Jan. 23, p. 228) had suffered the same treatment by the National Insurance set-up as myself. Dr. Edelston's prediction that to go on in an attempt to obtain redress is a waste of time and a foregone conclusion is only too true.

After the first refusal I elected to go before a "tribunal" over my claim. There were three members, and the chairman's opening gambit was that "if they leaned over backwards" there was nothing they could do about the matter. One's immediate reaction was to say, Why waste my time and yours then? In the letter I received a few days later informing me that the tribunal had turned down my appeal was a notice that I could have my claim sent to the Commissioner in London. This I did, and after some 3–4 months back came a long screed putting the points of my case, but of course ending with a refusal to allow my claim, so, after all this, we were where we started.

The whole thing is so unjust that I feel it needs thoroughly airing, and should be taken up in an attempt to get such infamous rules amended.

Lenham, Kent

W. A. HERVEY

AN ILLNESS OF INFECTION IN CHICKENPOX

SIR,—Dr. Partington (Jan. 16) has I see resurrected the suggestion made by my late chief, Dr. Edward Goodall, that an "illness of infection" occurs in measles, and he now puts forward his reasons for believing that a similar illness may occur in chickenpox as well.

If an "illness of infection" actually occurs within a day or two of infection with measles, then it can only mean that the body defences have been effectively challenged by a score or two of virus particles to produce a vigorous defence reaction but one that is curiously lopsided. For though the febrile component is well marked the antibody factories remain remarkably inactive. Otherwise the virus, when in due course it had penetrated its target cells, replicated a millionfold, and burst into the bloodstream, would find itself, like the variola virus in a smallpox contact vaccinated a few days after exposure, confronted with a flood of antibodies. But that does not happen here, the measles virus is in no way impeded and produces an attack of normal severity. If the "illness of infection" were followed by an attenuated attack—or sometimes none at all—it might be credible, but as things are it would seem to be quite purposeless. It is my general impression that the defence mechanisms of the body do not indulge in purposeless reactions.

However, leaving theory aside, I remember that when Goodall first published his views I was then one of his very new junior assistants and I was naturally anxious to verify his observations. Scope was abundant, because in those days with large open wards measles intrusion was common and exasperating. Before convalescent serum became available, two or three cases might occur every fortnight until the supply of susceptibles ran out, meantime valuable beds were inactivated for weeks on end. Diphtheria wards offered a particularly good field for observation as the disease was largely afebrile and the patients, although relatively long-stay, were kept under the strictest observation in view of possible complications. But it uon of oil or tooth particles under these

would endorse the statement in your ieral oils used for lubricating purposes a risk, mainly of lipoid pneumonia, and ss that the above remarks apply only to getable oil The question also arises of iination by the blast of air from the iave no observations as yet on this point ntly been informed that some dental xperienced irritation of the eyes and ollowing the use of an air-turbine drill, nterested to hear from others who have ntoward effects

ch in Industrial Medicine, search Council, spital, London, E 1 G KAZANTZIS E KING

ER ON BLOOD FIBRINOLYTIC ACTIVITY

sing experiments of Dr Fearnley and 23) suggest that drinking ten to forty everages reduces fibrinolytic activity, does not Is the lysis-time similarly ing ten to forty ounces of water, or

G I C INGRAM

ES IN HYPOCALCÆMIA

and Dr Garretts (Jan 16) state hypocalcæmia " it is the lowered main cause of the skin lesions " patient with idiopathic steator- make me believe that this state- ation of the facts as far as ncerned

was diagnosed by Dr Kenneth a with exfoliative dermatitis years before and had become had been progressive weakness ale, and almost bald. There d dusky brown pigmentation maceration and fissuring of and thickened There were s Chvostek's sign was % (2 2 g per 100 ml) er c mm plasma-protein in 3 9, globulin 2 1) rus 4 8 mg per 100 ml. -phosphatase 10 units hæmosiderin pigment to a slight extent in er-function tests and and follow-through testine The sugar-

folic acid, iron, h-protein gluten- greatly and the e corrected, and obtained work,

ted only of a n-calcium was , and hæmo-

ot improved l condition ion of pig- for some 5 years red and finely peeling, and with intermittent ulceration of his pachydermatous lymphœdematous ankles

I think it is right to regard his erythrodermia as having been caused by a gross and broad nutritional deficiency—of protein, vitamins, and iron, as well as of calcium The failure of his skin to recover conspicuously may be due to irreversible damage caused by the great severity and duration of his disease, but I attribute the degree of improvement that has occurred to the correction of his protein, vitamin, iron, and calcium deficiency and to the dietary gluten restrictions, but not to the correction of his calcium deficiency alone

London, W 1 BRIAN RUSSELL

INTESTINAL ABSORPTION OF VITAMIN B_{12} AND THE B_{12} COENZYMES

SIR,—Dr Wasserman and his associates[1] recently commented on the paper by Reizenstein and Nyberg[2] and mentioned some experiments with the 5,6-dimethylbenziminazolyl cobamide coenzyme ($B_{12\mathrm{Co}}$) isolated by Barker's group In this connection some of our experiments with non-labelled $B_{12\mathrm{Co}}$* may be of interest

(1) Four patients with genuine pernicious anæmia were submitted to Schilling tests in which intrinsic factor (20 ml of gastric juice) was given with 2 μg of radiovitamin B_{12} Before or after the mixing of the two, 15 μg of non-labelled B_{12} or $B_{12\mathrm{Co}}$ was added. The object was to study whether or not one of the two substances (B_{12} and $B_{12\mathrm{Co}}$) was absorbed preferentially in the presence of the other (cf Bishop et al[3]) Compared with non-labelled B_{12}, $B_{12\mathrm{Co}}$ had an equal or slightly weaker inhibitory effect on the absorption (urinary excretion) of radiovitamin B_{12} under the conditions used In other words, B_{12} and $B_{12\mathrm{Co}}$ diluted the isotope in about the same way This fits in with the finding[1] in studies with liver homogenates that B_{12} and $B_{12\mathrm{Co}}$ compete in a 1 1 ratio

(2) The binding of B_{12} and $B_{12\mathrm{Co}}$ to gastric juice was studied in vitro If $B_{12\mathrm{Co}}$ was added first and radioactive B_{12} afterwards, the binding sites were occupied by $B_{12\mathrm{Co}}$ and the subsequently added radiovitamin B_{12} was able to displace $B_{12\mathrm{Co}}$ from some 30% of the binding sites Under the same conditions $B_{12\mathrm{Co}}$ displaces about 10% of previously bound radioactive B_{12} Thus the affinity of B_{12} for the binding sites is somewhat greater than that of $B_{12\mathrm{Co}}$ In addition, the same electrophoretic fractions of gastric juice were found to bind both substances In these experiments binding was assayed with both exhaustive dialysis and adsorption of free B_{12} to resting bacterial cells Since $B_{12\mathrm{Co}}$ is light-sensitive all experiments were performed under as dark conditions as possible

Thus, our preliminary studies indicate that B_{12} and $B_{12\mathrm{Co}}$ behave in roughly the same fashion In view of the indirect way we studied $B_{12\mathrm{Co}}$ (no radioactive $B_{12\mathrm{Co}}$ was available to us), we do not know whether it is absorbed better than B_{12} Supposing both compounds are taken up by the same acceptor mechanism in the intestinal wall, preferential absorption of one would be expected to inhibit the absorption of the other However, in our experiments $B_{12\mathrm{Co}}$ did not inhibit the absorption of radioactive B_{12} even as much as non-labelled B_{12} did On the other hand, using radioactive $B_{12\mathrm{Co}}$ Dr Wasserman and his associates[1] found that the absorption of $B_{12\mathrm{Co}}$ is not so dependent on intrinsic factor as that of vitamin B_{12} This may perhaps be related to the weaker binding affinity of intrinsic factor preparations for $B_{12\mathrm{Co}}$

Minerva Foundation Institute
for Medical Research,
Helsinki Finland

RALPH GRÄSBECK
FRED BJORKSTEN

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[1] Wasserman L R , Estren, S , Brody, E., Herbert, V *Lancet*, Jan 16, 1960, p 173
[2] Reizenstein P G , Nyberg W *ibid* 1959, ii, 248
[3] Bishop, R C Toporek, M , Nelson, N A , Bethell, F H *J Lab clin. med* 1955, 46, 796
* Supplied by Dr H A Barker, Department of Biochemistry, University of California, Berkeley 4, California

HOTELS OR HOSPITALS?

SIR,—The stimulating articles in your issue of Jan. 9 by Mr Stallworthy (p 103) and your peripatetic correspondent (p 109) are timely Many of our present troubles are due to a perpetuation of medical thoughts and actions common before the N H S began, but still regarded as sacrosanct

There are still too many small hospitals of less than 100 beds, dissipating medical and nursing manpower This is a small country most patients are really not so far from large towns and the larger hospitals, which could well be made larger with the money saved in closing small and inefficient units

Road and other accidents are surely going to increase Many are treated in small general hospitals ill equipped to deal with them A nationwide accident service is urgently needed, perhaps based on hospitals such as the Birmingham Accident Hospital Again, local medical, if not lay, sentiments must be overcome

Long waiting-lists are commonly held responsible for delay in admission Not enough thought is being given to why some lists are longer than others, not only in different specialties but in the same specialty in different areas Again, little effort is made to revise lists at regular intervals Who should do this? Certainly not lay record officers It would be revealing to know how many patients on particular lists have moved or been treated elsewhere, who have died, who will have refused treatment, and, most important, who may not need treatment after all This type of investigation again depends largely on medical cooperation and would apply to such conditions as " tonsils ", chronic appendicitis, and D & C

As for the special problems of the fever hospital, it is true that many have empty beds, but when they are needed they are needed in a hurry Epidemics are unpredictable, and it is wishful thinking to say that they cannot happen here Surely the best analogy is the Fire Service, which equally ties up valuable manpower, material, and space

It is time that a more rational and less emotional approach to the value of good medical administration was adopted by all doctors Maybe this is a glimmer on the horizon

Chadwell Heath Hospital,
Romford, Essex

I M LIBRACH

TREATMENT OF GALACTOSÆMIA

SIR,—In reply to the letter from Dr Schwarz and his colleagues (Dec 19) we wish to apologise for an error which was overlooked in our letter of Nov 14 Galactose-1-phosphate was actually expressed as micromoles not as microgrammes If the values quoted in our letter are transferred to microgrammes it will be seen that the two sets of normals are in agreement

Their suggestion that soya meal should not be used until it is " proved " safe surely would prevent its being used at all Strict proof that stachyose is not digested by the human infant can at present be obtained only by giving it to a galactosæmic infant and showing that this does not lead to an accumulation of galactose-1-phosphate in the erythrocytes Since stachyose and other compounds containing galactose occur in various other foods besides soya which are used in the treatment of galactosæmia a considerable amount of testing of these different compounds would have to be carried out, and in view of the limited number of galactosæmic babies available such testing might well take several years to complete. In the meantime cases of galactosæmia are urgently needing treatment, and soya preparations may surely play a useful part as long as they are found not to cause an accumulation of galactose-1-phosphate in the erythrocytes

While the few cases we have so far treated with soya preparations cannot be taken to prove the safety of soya, such evidence as we have been able to get supports the belief that galactose is not liberated in sufficient amount to cause a measurable increase in the erythrocyte galactose-1-phosphate. Clinical observations unsupported by chemical tests cannot on a short-term basis be accepted as proof of either danger or safety The failure to gain weight (apparently due to gastro-intestinal disturbances) shown during a short period in the single case reported by Dr Schwarz and his colleagues need not have been due to galactose liberation. We have seen a similar picture frequently when very young infants are placed abruptly on a synthetic diet If the new diet is introduced gradually over several days intolerance can be avoided

The addition of different foods to the diet of a galactosæmic infant may introduce a possible source of danger, since many baby foods contain appreciable amounts of lactose or other compounds of galactose It is necessary to discover what foods are galactose-free Jones and Leak[1] have given some indications of this in a recent paper, and we are now starting a study of the galactose content of weaning foods which we hope may give useful results

The Hospital for Sick Children, Great Ormond Street, London, W C 1	W W PAYNE
University College Hospital Medical School, London, W C 1	T A J PRANKERD
Vegetarian Nutritional Research Centre, Stanborough School, Garston, Watford, Herts	FRANK WOKES

⁂At Dr Payne's suggestion we published a correction about the galactose-1-phosphate levels in our issue of Nov 28, but we failed to draw it to the notice of Dr Schwarz and his colleagues before publishing their letter We apologise to all concerned for our part in this misunderstanding —ED L

DENTAL DRILLS

SIR,—In your leading article of Jan 2 the possible risks to an operator using the new high-speed air-turbine instrument are discussed As you say, such risks may be caused by particles of tooth and old filling material propelled into the air by the blast of the turbine exhaust and by oil used in lubricating the turbine, which may be entrained in droplet form with the air-supply

Last year, at the request of Dr W G Senior, chief dental officer to the Ministry of Health, a preliminary investigation was carried out in this department on the environmental problems involved. An 'Alston' drill was used In this instrument, the turbine is powered by an airstream which first passes across a vegetable-oil drip feed, while a secondary air-supply directs a jet of water on to the head of the bur *At an operating air pressure of 40 lb per sq in* the turbine speed was found to be approximately 260,000 r p m under no-load conditions

We did not measure the sound output, but a crystal pick-up, making mechanical contact with the turbine head, off load, showed a fundamental vibration of 4400 cycles per second, with some distortion, but not enough to suggest the presence of a high percentage of harmonics Thus, the major sound emission can be expected at this frequency

In order to study atmospheric contamination *arising from* drilling, four teeth, mounted in a cavity *simulating the* human mouth, were drilled *continuously for 30 minutes*, with an oil flow *of 33 drops per minute*, and a water flow of 2 6 ml per min An air sample, taken at a point one foot in front of the " mouth " and six inches above it, showed an average concentration of 1 3 mg oil per cubic metre of air Microscopic examination of a cascade impactor sample showed that the greater mass of both the oil and particulate matter was trapped in drops of water larger than would usually be considered " respirable " A second sample, taken during ten minutes of drilling, showed a *calcium concentration* from the tooth particles of *100 µg per cubic metre of* air In actual practice *the drill would not be used* for as long as ten minutes, so that the concentrations obtained would be lower It was concluded from the experiment that there was little risk to the operator from the inhalation of oil or tooth particles under these circumstances.

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[1] Jones, N L, Leak, D *Arch Dis Childh* 1959, 34, 307

However, we would endorse the statement in your article that mineral oils used for lubricating purposes might provide a risk, mainly of lipoid pneumonia, and we wish to stress that the above remarks apply only to the use of a vegetable oil. The question also arises of bacterial contamination by the blast of air from the turbine, but we have no observations as yet on this point.

We have recently been informed that some dental surgeons have experienced irritation of the eyes and respiratory tract following the use of an air-turbine drill, and we would be interested to hear from others who have experienced any untoward effects.

Department for Research in Industrial Medicine,
Medical Research Council,
The London Hospital, London, E.1

G. KAZANTZIS
E. KING

EFFECT OF BEER ON BLOOD FIBRINOLYTIC ACTIVITY

SIR,—The appetising experiments of Dr. Fearnley and his colleagues (Jan. 23) suggest that drinking ten to forty ounces of alcoholic beverages reduces fibrinolytic activity, whereas two ounces does not. Is the lysis-time similarly prolonged by swallowing ten to forty ounces of water, or even air?

St. Thomas's Hospital,
London, S.E.1

G. I. C. INGRAM

SKIN CHANGES IN HYPOCALCÆMIA

SIR,—Professor Dent and Dr. Garretts (Jan. 16) state that in their cases with hypocalcæmia "it is the lowered calcium level that is the main cause of the skin lesions." Observations of a similar patient with idiopathic steatorrhœa and erythrodermia make me believe that this statement is an oversimplification of the facts as far as idiopathic steatorrhœa is concerned.

In July, 1954, a male of 22 was diagnosed by Dr. Kenneth Perry as idiopathic steatorrhœa with exfoliative dermatitis. His rash had begun some 8 years before and had become generalised. For 7 months there had been progressive weakness and pallor. He was emaciated, pale, and almost bald. There was generalised erythrodermia and dusky brown pigmentation of the skin, with ectropion, and maceration and fissuring of the flexures. The nails were rough and thickened. There were retinal hæmorrhages and exudates. Chvostek's sign was positive. The hæmoglobin was 15% (2.2 g. per 100 ml.), red cells 1,060,000, leucocytes 2400 per c.mm., plasma-protein 6.0 g. per 100 ml. (plasma albumin 3.9, globulin 2.1). Serum-calcium 6.6, inorganic phosphorus 4.8 mg. per 100 ml., acid-phosphatase 0.6 units and alkaline-phosphatase 10 units.

The liver biopsy showed an excess of hæmosiderin pigment mainly in the Kupffer cells, and also to a slight extent in parenchymal cells and portal tracts. Liver-function tests and blood-urea were normal. Barium meal and follow-through showed "steatorrhœa pattern" in small intestine. The sugar-tolerance curve was flat.

After treatment by blood-transfusion, folic acid, iron, vitamins, calcium lactate, calciferol, and a high-protein gluten-free diet, his general condition improved greatly and the anæmia and disturbance of serum-calcium were corrected, and have remained normal ever since. He has obtained work, maintaining television sets.

Since June, 1959, his treatment has consisted only of a gluten-free diet. In September, 1959, his serum-calcium was 10.4, inorganic phosphorus 3.6 mg. per 100 ml., and hæmoglobin 94% (13.8 g. per 100 ml.).

Unfortunately the condition of his skin has not improved pari passu with the great improvement in his general condition. After an initial improvement in texture, diminution of pigmentation and exfoliation, the skin has remained for some 5 years red and finely peeling, and with intermittent ulceration of his pachydermatous lymphœdematous ankles.

I think it is right to regard his erythrodermia as having been caused by a gross and broad nutritional deficiency—of protein, vitamins, and iron, as well as of calcium. The failure of his skin to recover conspicuously may be due to irreversible damage caused by the great severity and duration of his disease, but I attribute the degree of improvement that has occurred to the correction of his protein, vitamin, iron, and calcium deficiency and to the dietary gluten restrictions, but not to the correction of his calcium deficiency alone.

London, W.1

BRIAN RUSSELL

INTESTINAL ABSORPTION OF VITAMIN B_{12} AND THE B_{12} COENZYMES

SIR,—Dr. Wasserman and his associates[1] recently commented on the paper by Reizenstein and Nyberg[2] and mentioned some experiments with the 5,6-dimethyl-benziminazolyl cobamide coenzyme ($B_{12_{Co}}$) isolated by Barker's group. In this connection some of our experiments with non-labelled $B_{12_{Co}}$* may be of interest.

(1) Four patients with genuine pernicious anæmia were submitted to Schilling tests in which intrinsic factor (20 ml. of gastric juice) was given with 2 μg. of radiovitamin B_{12}. Before or after the mixing of the two, 15 μg. of non-labelled B_{12} or $B_{12_{Co}}$ was added. The object was to study whether or not one of the two substances (B_{12} and $B_{12_{Co}}$) was absorbed preferentially in the presence of the other (cf. Bishop et al.[3]). Compared with non-labelled B_{12}, $B_{12_{Co}}$ had an equal or slightly weaker inhibitory effect on the absorption (urinary excretion) of radiovitamin B_{12} under the conditions used. In other words, B_{12} and $B_{12_{Co}}$ diluted the isotope in about the same way. This fits in with the finding[1] in studies with liver homogenates that B_{12} and $B_{12_{Co}}$ compete in a 1 : 1 ratio.

(2) The binding of B_{12} and $B_{12_{Co}}$ to gastric juice was studied in vitro. If $B_{12_{Co}}$ was added first and radioactive B_{12} afterwards, the binding sites were occupied by $B_{12_{Co}}$ and the subsequently added radiovitamin B_{12} was able to displace $B_{12_{Co}}$ from some 30% of the binding sites. Under the same conditions $B_{12_{Co}}$ displaces about 10% of previously bound radioactive B_{12}. Thus the affinity of B_{12} for the binding sites is somewhat greater than that of $B_{12_{Co}}$. In addition, the same electrophoretic fractions of gastric juice were found to bind both substances. In these experiments binding was assayed with both exhaustive dialysis and adsorption of free B_{12} to resting bacterial cells. Since $B_{12_{Co}}$ is light-sensitive all experiments were performed under as dark conditions as possible.

Thus, our preliminary studies indicate that B_{12} and $B_{12_{Co}}$ behave in roughly the same fashion. In view of the indirect way we studied $B_{12_{Co}}$ (no radioactive $B_{12_{Co}}$ was available to us), we do not know whether it is absorbed better than B_{12}. Supposing both compounds are taken up by the same acceptor mechanism in the intestinal wall, preferential absorption of one would be expected to inhibit the absorption of the other. However, in our experiments $B_{12_{Co}}$ did not inhibit the absorption of radioactive B_{12} even as much as non-labelled B_{12} did. On the other hand, using radioactive $B_{12_{Co}}$ Dr. Wasserman and his associates[1] found that the absorption of $B_{12_{Co}}$ is not so dependent on intrinsic factor as that of vitamin B_{12}. This may perhaps be related to the weaker binding affinity of intrinsic factor preparations for $B_{12_{Co}}$.

Minerva Foundation Institute
for Medical Research,
Helsinki, Finland

RALPH GRÄSBECK
FRED BJORKSTEN

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[1] Wasserman, L. R., Estren, S., Brody, E., Herbert, V. *Lancet*, Jan. 16, 1960, p. 173.
[2] Reizenstein, P. G., Nyberg, W. *ibid.* 1959, ii, 248.
[3] Bishop, R. C., Toporek, M., Nelson, N. A., Bethell, F. H. *J. Lab. clin. Med.* 1955, 46, 796.
* Supplied by Dr. H. A. Barker, Department of Biochemistry, University of California, Berkeley 4, California.

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—In view of the comments that my letter of Jan 2 provoked, may I be allowed to enlarge on certain aspects?

In reply to Mr Murley (Jan 9), there were 1752 cases of cavernous angiomas or nævi and 814 cases were given superficial X-ray therapy No attempt was made to analyse this series in detail, for the paper quoted would have been as long as the original article by Dr Simpson (Dec 12)

My letter was not even a criterion of this excellently produced article, but merely to call attention to another viewpoint Do cavernous nævi across the Atlantic behave so differently from those in this country? I would consider American documentation quite our equal

I entirely agree with Dr Sneddon (Jan 16) that it is far easier to treat than to adopt an attitude of masterly inactivity, but there is surely some place for a mother's peace of mind to know that something is being done and that the disfigurement will go from baby in the minimum of time

My practice has been to treat all such lesions with thorium X varnish (2500 e s u per ml) once per month, and only where there was increase in size or failure to satisfy the parents, resort to superficial X-ray therapy

In reply to Dr Moynahan (Jan. 23) none of the cases given superficial X-ray treatment was given more than 1200r units, and the majority reacted satisfactorily to smaller doses

I, too, examined many troops in the past war, although I could not claim to have seen 100,000 men, unless it was a march past. I admit I too saw no evidence of cavernous nævi, but this is easily explained because I was not looking for signs of them, and the same applies to Dr Moynahan.

I see their evidence now because I am looking for them, and can only offer Dr Moynahan an invitation to spend a pleasant weekend with me at the seaside and show him a few, commencing with one of my own sons

This brings me to another point. Is it a good treatment to leave a child up to the age of 5 or 7 with a disfiguring blemish even if it is going to disappear spontaneously? Psychiatrists would have very strong views on this

I am convinced that superficial X-ray treatment reduces to a minimum the cases of spontaneous ulceration, and of course it is the subsequent scarring of these one sees later in life

In my own child, contrary to my judgment, I followed the advice of no treatment, spontaneous ulceration occurred, and there is certainly no maternal satisfaction, which I would remind Dr Moynahan was the criterion of cure Does he produce this by doing nothing? I cannot believe it

May I remind readers that no dermatologist can have seen more children than Dr R. T Brain, of Great Ormond Street, and it has always been his practice to give superficial X-ray therapy where necessary In a reported series of 614 cases[1] 147 lesions were untreated and they cleared up nearly as well, although not so quickly

I can think of many patients over the past 15 years who were dissatisfied with the rate of progress, but ready to wait patiently Very few would have been satisfied to sit back and see nothing done, and moreover the vast majority of family practitioners are relieved to know that these cases are being taken in hand

It can never be the genuine view of any that nothing active must be done, for several of the cavernous nævi in Dr Millington's and my series interfered with feeding, breathing, and vision Do our advocates of no treatment employ pipette or tube feeding, let the respiratory embarrassment remain, or allow the baby to grow up with monocular vision?

I am grateful to Mr Denis Browne for the reproductions accompanying his letter of Jan 30 These illustrate very adequately the type of angioma that leaves persistent deformity

I am also grateful to Dr Brian Russell (Jan 30) for his excellent series, but here again I consider he supports our view If this baby had been his own child would he be prepared to just look at it for 6 years and do nothing? Would he be proud as father and dermatologist of his disfigured offspring? What about the mother's wishes, and I very much doubt if the last three blank spaces will show an absolutely normal lip—when he starts school his playmates will pull it and upset him

One of my surgical colleagues has just told me of a case that recently came under his care and was referred by him to the Royal Marsden Hospital The diagnosis was carcinoma of the thyroid and alleged to have followed X-ray therapy for a nævus, but he took the trouble to inquire exactly concerning this and found to his surprise that only thorium-X varnish had been used and no X-ray treatment given I imagine even the die-hards would hesitate to blame this form of radioactivity

Hove E COLIN-JONES

SIR,—I agree with Dr Ray Bettley (Jan 23) that the application of carbon-dioxide snow for 15 seconds will abolish a small superficial lesion, usually with a good cosmetic result, but unfortunately, especially on the face, an unpleasant and permanent dead-white scar occasionally results This is very uncommon after short applications, but I have seen it several times and am therefore reluctant to use such treatment It is much more debatable whether snow will "gradually improve all the rest" It is usually possible to decolorise the surface, but the deeper parts of thick lesions may persist, and accidents can happen

My teacher, Dr Sydney Thomson, once advised me that the first application of snow to a cavernous hæmangioma should never be for more than 5 seconds, with minimal pressure, in case of idiosyncrasy Although I now seldom use such treatment, I was recently prevailed upon by an anxious mother and a persuasive doctor to apply snow for 5 seconds to part of a lesion covering an infant's patella The resulting sloughing ulcer took six months to heal, after which the child required admission to hospital for manipulation before it could be induced to move its knee The end result was an unsightly scar in and around the treated area with spontaneous disappearance elsewhere

It is because of cases of this type, admittedly unusual, that I cannot agree that such treatment is "so simple, safe and effective that one wonders why anyone should wish to withhold it" This is, in effect, what Dr Colin-Jones and others have said of radiotherapy, yet most of us prefer to avoid it in so benign a condition, however rare unfortunate results may be

Hythe, Kent DENIS SHARVILL

SIR,—This very interesting discussion may be a vindication for "clinical impressions" as compared with statistics, for the value of which we have the opinion of Benjamin Disraeli I have read all the contributions with reasonable care, but nowhere can I find mention of the possibility of the "cavernous hæmangiomata" becoming malignant in after years This outcome must be rare, but it does happen, and is therefore a point in favour, perhaps, of operation I have seen one such case, in a girl aged three years, who had her "cavernous hæmangioma" removed at operation, only to succumb to a sarcoma, primary in the operation scar, about the age of fifteen.

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[1] Brain, R T, Calnan, C D *Brit J Derm* 1952, 64, 147

The obvious course seems to be, " keep the patient under observation " for many years if possible One advantage of operation is that sections can be studied, much can be learnt from careful study

St Margaret's Hospital,
Epping

FRANK MARSH

SIR,—Will you please allow me to thank all of your correspondents who have shown such an interest in my paper on this subject and to make a few comments?

My aim was to provide more factual information, in rather more detail than had been published before, for the benefit of those who have already seen the light and whose chief concern in the early stages is to allay parental anxiety The subsequent correspondence confirms my statement that the majority of dermatologists in this country agree with the views I expressed and it is reassuring to learn that both general and plastic surgeons are following the same policy

With regard to nomenclature I claim neither originality nor authority but merely tried to define the terms used

The point raised by Mr Denis Browne as to whether really early treatment of small lesions is justifiable or not can only be decided by investigations, such as I and others have been attempting in the past thirty years, and it is disappointing that Mr Browne can deduce so little evidence in favour of his very definite opinion in favour of treatment.

The only evidence I can offer is that out of 25 lesions of more than 3 cm. diameter 11 (44%) had disappeared without trace at 5 years and the others were all resolving satisfactorily, moreover in only 10 of these 25 cases had the lesion grown rapidly, i e., faster than the child. Like Dr Dowling, I have never seen a really large hæmangioma arise from a tiny spot. On the other hand, last year I saw an infant with over 100 small dermal lesions, of which none grew as large as 1 cm in diameter and all showed signs of resolution by the 6th month

Surely a few years' maternal embarrassment is of less importance than the patient's cosmetic appearance in adult life.

Exeter

J R. SIMPSON

KURU AND SPORADIC TREMOR SYNDROMES IN NEW GUINEA

SIR,—Wilson et al[1] reported 24 cases of various tremor syndromes found sporadically in a population of about 100,000 natives in the Western Highlands of New Guinea and they have described 3 of these cases as examples of a kuru-like syndrome They believe that " the implications of these newly discovered neurological disorders for the kuru problem are great " In fact, they go on to say, " If the genetic hypotheses are correct, Melanesian natives may possibly have an unstable locus in their chromosomes at which mutation to produce inborn defects of metabolism leading to cerebellar, basal-ganglionic, and generalised central-nervous-system diseases of the kuru type is likelier than among other races " Later on, after making what appears to be a contrary suggestion that " a single kuru mutation might be assumed to underlie both syndromes ", they say " the ethno-environmental variables which determine altered clinical and epidemiological expression must be elucidated " I think it needs to be made clear that no supporting evidence for these various genetic ideas has been put forward

No genetic investigation has been described for these sporadic tremor syndromes And there is no justification for assuming that the genetic hypothesis which has been put forward and found to hold for kuru[2-4] should also be charged with accounting for these different rare tremor syndromes found in another part of the island Some of these disorders may indeed have a genetic basis but this awaits demonstration. It is unlikely that a genetic study could be made quickly, for the mere accumulation of genetic data for such sporadic disorders would probably be a very slow business But even if some of these syndromes should be shown to have a genetic basis and this did depend, in fact, on a single locus, this would provide no support for the view that an " unstable locus " is involved. Furthermore, one can entertain such a suggestion only by ignoring the distinctive and significant family patterns in respect of kuru which have been found throughout the region concerned.[2-4] A high mutation rate at the kuru locus would not help to explain the astonishingly high frequency of kuru in the Fore population of the Eastern Highlands—surely the most puzzling and significant feature of the whole kuru population problem.

The population genetics situation presented by kuru may be unique, but our understanding of this tragic situation will not be advanced by confusing this uniqueness with a high degree of improbability for a genetical cause for which there is no evidence In contrast with the suggestion made by Wilson et al that these new syndromes may be " clinical variants of kuru and related to it in pathogenesis ", may I express the hope that further work will enable those workers to make a clear distinction between these sporadic syndromes and kuru—as indeed they are already distinguished in a number of important ways

Department of Genetics,
University of Adelaide.

J H BENNETT

MEDICAL NEEDS OF INDIA

SIR,—Your interesting and sympathetic leader last week refers to the scheme of postgraduate training " going back to a committee formed in 1941 under the chairmanship of the late Sir Bennett Hance "

The Commission of Inquiry into Future Health Needs of India was in fact presided over by the distinguished Indian statesman, Sir Joseph Bhore The Bhore Commission was composed of individuals drawn from many walks of life—political, financial, sociological, and medical —and obtained evidence from an impressive array of witnesses from India and oversea, including an advisory body from England under the late John Ryle, with Janet Vaughan and Weldon Dalrymple-Champneys, Professor Ognev from Moscow, and others from America and Australasia

The Bhore report is a classic in the assessment of medical needs of an underdeveloped country

London, S W 1

GEORGE R. MCROBERT

NEW WORDS REQUIRED

SIR,—In response to Mr Caplan's request (Oct. 31), I suggest he may wish to consider a variation on the root word *errare*, to wander

In current usage, aberrations are " slight deviations from the normal course " to navigators, while to astronomers an aberration is " a slight apparent shifting in position of a heavenly body ", so the root word " aberrant " seems to be a natural choice for Mr Caplan's purpose

My suggestion is the neologism " aberract " to denote a variation from optimum conduct

Physical Restoration Division,
Department of Public Health,
Regina, Saskatchewan

D F CLARK
Administrative Director

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[1] Wilson, K., Zigas, V, Gajdusek, D C *Lancet*, 1959, ii, 699

[2] Bennett, J H., Rhodes, F A, Robson, H N *Aust Ann Med* 1958, 7, 269

[3] Bennett, J H., Rhodes, F A., Robson, H N *Amer J hum Genet* 1959, 11, 169

[4] Bennett, J H, Gray, A J, Auricht, C O *Med J Aust* 1959, ii, 505

Parliament

Population (Statistics) Bill [1]

Dr Edith Summerskill regretted that in introducing this Bill to the Commons on Feb 1 Miss Edith Pitt, parliamentary secretary to the Ministry of Health, had not explained more frankly the reasons why powers were sought to obtain further information about stillbirth and fœtal abnormalities, the age of fathers, and the duration of pregnancy Dr. Summerskill thought that the information asked for in the schedule made it clear that the Bill was related to the genetic effect of nuclear radiation The Minister had never been persuaded to admit that the increase in congenital abnormalities and in the incidence of leukæmia might be partially due to radioactivity, Yet here they had a Bill the import of which every scientist would know precisely, and an opening speech which had not for one moment touched on the real reason for its introduction

Mr Derek Walker-Smith agreed that part of the object of the Bill was to find out more about the incidence of congenital abnormalities They were acting on the advice of the Medical Research Council Even if the number of mutational births was very small indeed, nevertheless there was something here which we had to study The Medical Research Council was anxious to study it, and the Government were anxious to give the Council the facilities and scope under this Bill which would enable it do so

QUESTION TIME

Preludin (Phenmetrazine)

Dr. Edith Summerskill asked the Minister of Health whether he now proposed to prohibit the sale, without medical prescription, of 'Preludin' —Mr Walker-Smith replied The Home Secretary, as an interim and urgent measure, has asked the Poisons Board to advise him which of the substances referred to by the Interdepartmental Committee should be limited to supply on prescription, under the Pharmacy and Poisons Act, 1933 The Poisons Board has held a meeting to consider the matter and he expects its report very shortly Dr Summerskill May I remind the Minister that the whole question of the administration and consumption of this dangerous drug, preludin, was considered in this House a year ago after comments had been made in a coroner's court? Since then, there have been other fatalities Could he not at least prohibit the sale of this drug without medical prescription? Will he read the report on the drug industry by a subcommittee of the Senate in the United States? In view of the fact that American firms are making such headway in this country, should we not take warning from the revelations which were made to the Senate last week?—Mr Walker-Smith The question of this drug can be dealt with only under the procedure of the Pharmacy and Poisons Act, 1933 An interim report by the Interdepartmental Committee was received on Jan 21, the Poisons Board has already met, and the Home Secretary will be very shortly making his statement in regard to action

Working Party on Legislation on Medicines

Mr Gresham Cooke asked the Minister if he would give particulars about the Interdepartmental Working Party which he had set up on legislation concerning medicines —Mr Walker-Smith replied This Working Party has been set up by the Secretary of State for Scotland and myself, in consultation with the Home Secretary, with the following terms of reference

> "to review the legislative provisions which relate to the control of medicinal substances and to recommend what changes should be made to rationalise and simplify the law with a view to ultimate amendment and consolidation"

It consists of 12 officials from the Government departments mainly concerned, of whom 2 have medical, 3 legal, and 2 pharmaceutical qualifications, and it will receive evidence from the organisations that are expert in this field

Hostels for Mental Patients

Mr N N Dodds asked the Minister what progress was being made in providing hostels for people now confined in mental hospitals solely because there was no other provision for their welfare, in view of the desirability of enabling them to regain their liberty and self-respect as members of the community —Mr. Walker-Smith replied Local authorities have made a start in providing hostels of various kinds for the mentally disordered It is likely that the main effect at first will be to avoid hospital admission for those not in need of it rather than to enable hospitals to discharge patients, local authorities and hospital authorities have, however, been asked to consult together in assessing future needs for the provision of hostels

Poliomyelitis and Infective Hepatitis

Mr L. A. Pavitt asked the Minister of Health what was his department's policy regarding the treatment of poliomyelitis and infective hepatitis in open wards Mr Derek Walker Smith replied I have conveyed to hospital authorities the view that patients with any infectious disease should normally be nursed in isolation and recommended certain precautions to be observed when it is necessary to nurse such patients in open wards I have suggested that special hospital units should be provided where practicable for the treatment of poliomyelitis

University Places

Mr Malcolm MacPherson asked the Chancellor of the Exchequer, with reference to his announcement on Feb 20, 1958, of a building programme for the universities for 1960-63, related to an estimated rise of student numbers to 124,000 in the mid-1960s, with the possibility of a further increase of 10% in the second half of the decade, whether he would not consult with the University Grants Committee as to the desirability of relating the building programme to higher numbers than these —Mr Heathcoat Amory replied The University Grants Committee last year made a full examination of this question in the light of the latest estimates of future numbers of seventeen and eighteen-year-olds in the schools and of other relevant factors As a result they recommended strongly to me that they should be authorised to discuss with the universities an expansion of their capacity beyond the figure of 135,000 places which had already been agreed They proposed to explore the possibility of providing an additional 35,000 to 40,000 by the late 1960s or early 1970s and to etsimate the capital cost involved I have authorised this action and I understand that discussions with the universities have already begun

Approved School Inquiry

In a statement on the recent report on the disturbances at an approved school, Mr R A Butler, the Home Secretary, said that it included some general recommendations not requiring legislation With these he was broadly in agreement, especially on the need for securing an adequate number of trained housemasters, and for pressing forward with plans for modernising and improving accommodation He agreed also with the view that a limited provision of secure facilities was necessary to deal with the minority of difficult and troublesome boys with a disruptive influence on normal training

The proposals involving legislation presented greater difficulty, and needed consideration in relation both to the legislation about the treatment of young offenders, which was foreshadowed in the Gracious Speech, and to the wider questions affecting approved schools The Ingleby Committee had also under consideration some aspects of these questions He would therefore prefer to defer further comment on the proposals for amending legislation until he had considered them in relation to his suggestions in the whitepaper He was sure that the House would wish him to make comprehensive proposals for the treatment of young offenders, even if this involved some delay in introducing the Bill which was being prepared

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[1] See *Lancet*, 1959, ii 976

Obituary

WU LIEN-TEH

M A , M D Cantab , LL.D

PHYSICIAN to the Emperor and successive Presidents of China, director of the Manchurian plague prevention service, and director of the Chinese National Quarantine Service are unusual appointments for a Cambridge graduate to hold, but Dr Wu was an unusual man Fifty years ago, by his dramatic conquest of an outbreak of pneumonic plague in Northern Asia, he won an international reputation, he retained and enhanced it by his later work as a scientist, administrator, and writer

He was born in 1879 in Penang where his father was a goldsmith As one of a family of eleven children he had to make his own way in the world, but he won a Queen's scholarship, open to all the Straits Settlement, and he entered Emmanuel College, Cambridge, in 1894 At Cambridge, and indeed until he moved to China, he used the Cantonese-Malayan form of his name and was known as Gnoh Lean-Tuck. He took a first-class in the natural sciences tripos and in 1902 qualified from St. Mary's Hospital With a research studentship from his own college he continued his bacteriological studies at the Liverpool School of Tropical Medicine, the Pasteur Institute in Paris, Halle University, and the Selangor Institute at Kuala Lumpur In 1904 he returned to Penang and spent three years in general practice

In 1907 he was invited to join the Chinese Government service at Tientsin and in 1908 he became vice-director of the Army Medical College In 1910 he was sent by the Manchu Imperial Government to Harben to try to suppress a virulent epidemic of pneumonic plague that was killing over 100 people a day He was given a dangerous and desperate task, for he had to organise plague hospitals and a plague service out of nothing

In his autobiography, *Plague Fighter*, which appeared last year, he has described the desolate scene the ground was covered with snow as far as he could see, and dotted here and there were groups of destitute refugees coughing and spitting blood—candidates for certain death Wu had no protection, not even a mask, and his associates had no idea of the dangers of droplet infection They stood before the unfortunate victims, huddled into corners, and breathed in their breath Small wonder that nearly half the doctors and nurses died It was impossible to bury the dead, for the ground was frozen iron-hard Instead, they had to build high funeral piles and burn the corpses soaked in paraffin

By organising medical assistants, nurses, and orderlies, by separating contacts, by isolating the sick, and by fumigating the homes Wu succeeded in three months in controlling the outbreak. He also succeeded, as he reported at the International Congress on Plague over which he presided at Mukden in 1911, in tracing the infection to the marmot hunters—poor men who hunted the giant marmot (or tarabagan) and caught the infection from the pelts hanging in their miserable huts The tarabagan and the allied species of suslik were recognised as reservoirs of plague in the steppes and deserts of Manchuria and Siberia

In 1912 the Manchurian Plague Service was set up and inevitably Wu became its first director The Government allocated large sums for plague hospitals and the service became in effect a pioneer public-health service Wu's classical treatise on *Pneumonic Plague* was published in 1926 In 1930, when the National Government established a quarantine service, Dr Wu became director and equipped quarantine stations along the Chinese coast and at all important ports He retired in 1937 to Ipoh, where he had begun his medical work, and there he continued in practice throughout his alert and active retirement He died on Jan 21

During his varied life Wu received varied honours He was a mandarin of the second rank and an honorary graduate of Johns Hopkins University He had been decorated by the Czar of Russia and the President of France He sat on many advisory committees of the League of Nations and he was a founder of the Chinese Medical Association Of this versatile man P M -B writes

" Whatever the politics or whatever the revolution in his country, Wu lived and worked through it all He was a world authority on the opium trade, and he was interested in cholera, anthrax, narcotics, quarantine, and venereal diseases He never stopped writing, he attended every available medical congress in every continent, and he was known to everyone He never forgot his English friends, and he would turn up in London, now and then, to take up the threads, reminisce on his undergraduate days, and tell of his heroes, amongst whom he numbered Patrick Manson and Andrew Balfour In his massive autobiography, which is full of stories of his adventures, he showed himself as the great family man, proud of his family, proud of his offspring, and always proud of his Western contacts and forgiving for the sins of his European friends "

SAMUEL RONALD SINCLAIR

M B , B Sc Belf , F R C S E , D O M S

Mr S R Sinclair, ophthalmic surgeon to the Royal Victoria Hospital, Belfast, died on Jan 18, while on holiday in London He was 47 years of age

He was the youngest son of the late Mr Samuel Sinclair, of Cadogan Park, Belfast, and was educated at the Royal Academical Institution and Campbell College, Belfast, where he played in the rugby XV and the cricket XI He graduated B SC at Queen's University in 1933 and took his medical degrees three years later He was a house-physician in St Thomas's Hospital, London, before the war, and in 1939 he joined the R.A M.C and served in the Middle East as a specialist in ophthalmology with the rank of major On his return he took the F R.C S E in 1947 and was appointed a consultant by the Northern Ireland Hospitals Authority He was on the staff of the Royal Victoria Hospital (where he was honorary secretary of the medical staff committee), of the Ophthalmic Hospital, Belfast, and of other hospitals in the Province At Queen's University he was a clinical lecturer in ophthalmology

T W D writes

" Sam Sinclair was a scratch golfer who captained the University team in 1936 and won the Irish mixed foursomes championship in the same year He was a member of the Royal Belfast and Royal County Down Clubs and of Strangford Lough Yacht Club His skill, efficiency, equanimity, friendliness, his quiet manner, and sterling character endeared him to all of his colleagues, the nursing staff, and his patients in whom he took a deep personal interest "

Mr Sinclair leaves a widow and three daughters

EDWARD WEISS

M.D Jefferson

Dr Edward Weiss, professor of clinical medicine at Temple University School of Medicine, Philadelphia, has died at the age of 64 He was a founder and past president of the American Psychosomatic Society

H R R , who in 1953 as a Fulbright scholar worked with Dr Weiss in Philadelphia, writes

" It was an inspiration to discuss with him any problem in psychosomatic medicine, for he had a profound knowledge of clinical medicine and dynamic psychiatry and a razor-like intelligence He had a way of formulating his opinions, both verbally and in writing, so that they appeared on the surface disarmingly simple In his most recent book, *Don't Worry About Your Heart*, which was meant for the intelligent lay public, this adroitness is beautifully brought out

" Edward Weiss was highly cultivated, a superb host, and a most generous friend and colleague Among the social organisations to which he gave his time and skill were the Family Society of Philadelphia and the Marriage Council of Philadelphia He was an earnest Anglophile, and in one of my last conversations with him only last December he outlined his plan to return to England in the next year or so to explore and paint the Cotswolds "

Diary of the Week

FEB 7 TO 13

Monday, 8th

Postgraduate Medical School of London, Ducane Road W 12
4 P M Mr N W Please Elements of Statistical Methods
Guy s Hospital Medical School, S E 1
5 30 P.M Prof Russell Fraser Hyperparathyroidism
University of St Andrews
4 P M (Queen s College, Dundee) Dr J M Dodd, Mr K Ferguson Methods of Assay of Thyroid Stimulating Hormone and its Applications

Tuesday, 9th

Royal Society of Medicine, 1, Wimpole Street, W 1
5 30 P M *Experimental Medicine and Therapeutics* Dr A G Spencer, Dr G C Kennedy, Dr C T Dollery Chlorothiazide
7 30 P M *Psychiatry* Dr W B Scoville (Connecticut), Mr G C Knight, Mr W S Lewin, Dr R G McInnes, Dr J S I Skottowe, Dr P Macdonald Tow, Dr D W C Northfield, Dr J A N Corsellis Selective Neurosurgical Operations in Psychiatry with Special Reference to Orbital Undercutting
British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr R D Harkness Liver Regeneration
St Mary's Hospital Medical School, W 2
5 P M Mr Keith Vartan Implications of Blood Pressure on Pregnancy
Institute of Dermatology, Lisle Street, W C 2
5.30 P M Dr C D Calnan Allergy and Immunology with Reference to the Skin
Manchester Medical Society
8 P M (Clinical Sciences Building, York Place, Manchester) *Surgery* Mr F S A Doran Rupture in the Groin Mr W J Metcalfe The Low Operation for Femoral Hernia
Leeds Neurological Sciences Colloquium
5 15 P M (General Infirmary at Leeds) Prof G H Lathe Metabolic Contribution to Disease of the Brain
University of St Andrews
5 P M (Queen's College, Dundee) Prof A C Lendrum Photomicrography

Wednesday, 10th

Royal Society of Medicine
4 30 P M *Physical Medicine* Dr J G Parish, Dr C D Calnan, Dr J S Lawrence Heritable Disorders of Connective Tissue
8 P M *Proctology* Mr W B Gabriel, Mr T McW Millar, Mr W H Bond, Mr Gordon Ramsay, Dr Basil Morson Squamous Cell Carcinoma of the Anus and Anal Canal
Royal Free Hospital, Gray's Inn Road, W C 1
5 15 P M Prof M Rachmilewitz (Jerusalem) Liver and Vitamin B_{12} Metabolism
Institute of Dermatology
5 30 P M Dr R. W Riddell Antibiotics and Fungous Infections
Institute of Diseases of the Chest, Brompton, S W 3
5 P M Prof A. L. Cochrane Epidemiology of Coalworkers' Pneumoconiosis
Manchester Medical Society
5 P M (Medical School, University of Manchester) *Pathology* Dr H Lempert Treatment Control and the Pathologist (Presidential address)
University of St Andrews
2 30 P M (Queen s College, Dundee) Dr P B Marshall Value of Catechol Amine Assays—Adrenaline and Noradrenaline Metabolism

Thursday, 11th

Royal College of Surgeons of England, Lincoln's Inn Fields, W C 2
5 P M Dr B L Coley Tumours of Cartilaginous Origin (Moynihan lecture)
University College, Gower Street, W C 1
5 P M Dr Elizabeth Work Mucopeptides of Bacterial Cell Walls (Second of two lectures)
British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine) Dr A T James Factors Affecting Blood Lipid Composition
Institute of Dermatology
5 30 P M Dr S C Gold Non-tuberculous Granulomas
Institute of Laryngology and Otology, 330, Gray's Inn Road, W C 1
5 30 P.M Dr I Doniach Diseases of the Thyroid Gland
Alfred Adler Medical Society
8 P M (1, Wimpole Street, W 1) Dr D N Parfitt Reflections on Fear and Learning
North Western Thoracic Society
5 P M (Clinical Sciences Building Manchester) Dr Donald Longson Steroid Therapy Dr M O Connor Radiation Hazards and the Chest Physician Dr J C P Weber Long-term Chemotherapy in the Elderly
University of St Andrews
5 P M (Queen s College, Dundee) Dr Ian Gordon Rheumatic Disease in the Elderly Polymyalgia Rheumatica

Friday, 12th

Institute of Laryngology and Otology
5 30 P M Mr William McKenzie Use of Rosen s Approach in Diagnosis and Treatment
Institute of Neurology, National Hospital, Queen Square, W C 1
4 30 P M Dr G Ettlinger Recent Ablation Studies in the Monkey
Royal College of Surgeons of Edinburgh, 8
3 30 P.M Prof L N Pyrah Aspects of Renal Calculus

Notes and News

WORLD HEALTH ORGANISATION

SPEAKING to the Executive Board on the malaria eradication campaign, Dr M. G Candau, director-general of the World Health Organisation, said "we had no illusions that the campaign would be easy, but the problems are being solved and if eradication fails it will be not for technical reasons but because we have not got the money to carry it out."

According to information received by W H O from Governments, of the 1,238 million people that lived in originally malarious areas of the world, 258 million had been freed from this menace by the end of last year Another 641 million live in the 65 countries and territories where eradication programmes are in progress, and 95 million are in 33 countries and territories which have realistic plans for such programmes The board was told that the problem of mosquitoes becoming resistant to residual insecticides has proved not to be insurmountable and affects only 30 million people or less than 5% of the total number in areas where eradication programmes are in progress

Mr M Siegel informed the board that there was an estimated shortage of 1 3 million dollars to finance W H O's share of costs of malaria eradication for 1960 as at present planned, and that 6 4 million was needed to ensure continuation of the work in 1961, even at the slightly slower rate of progress that had been projected He deplored a situation in which over 95% of the 11 6 million dollars received before the end of 1959 had come from one member Government—that of the United States Among the other countries that had contributed, few were among the more economically developed, and some had the lowest per-capita incomes of the world During the discussion the situation was improved by the announcement of a new contribution by the U S S R of 1 million roubles in services and supplies, and another of £15,000 by Australia. The Government of Norway intends to propose a contribution of 100,000 dollars to Parliament as soon as W H O can announce that a certain number of other member States will contribute sums of the same relative size A contribution of 1 million German marks from the Government of West Germany is also foreseen, and on Jan 26 the board learned that the Canadian Government is asking Parliament for a contribution of 100,000 dollars

The United States has made the first donation (300,000 dollars) to W H O's Special Account for Community Water Supplies which was set up last year to give technical assistance to Governments

W H O's intensified programme of medical research was commended by Prof Lowell T Coggeshall (University of Chicago) as "intelligent" and practical It will give high priority to services to research—e g , the standardisation of nomenclature, techniques, and equipment, the establishment of reference centres for the identification of microorganisms, tissues, parasites, &c , and the improvement of communications among research-workers and of their training Next in priority will come demographic studies of the prevalence of diseases, and international coordinated research projects that may have a bearing on major W H O programmes

The hope was expressed that such research will tie nations together, establishing official contacts between research units that formerly only individuals achieved This is already being done by bilateral agreements, Dr Candau told the board, citing the agreement between the U S S R and the U S.A providing for, in part, exchanges of experience in the field of health and medical science[1] Dr Candau hoped that this move will lead to worldwide cooperation on a similar level, both Governments using W H O to bring other countries into the sphere of their cooperative efforts Prof V M. Zhdanov (U S S R) said that scientific institutions all over the world must further W H O's research programme He predicted that in time it will become one of the most important activities of the Organisation

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[1] See *Lancet*, Jan 23, 1960, p 233

The Government of India has invited W H.O to hold the Fourteenth World Health Assembly in New Delhi in 1961 Though the Assembly usually meets in May, this meeting will probably take place in February, when the Delhi climate will be more propitious

COST OF PHARMACEUTICAL SERVICES

In his review of the Appropriation Accounts for 1958–59[1] the Comptroller and Auditor General notes that the continuous increase in the cost of the pharmaceutical services of the National Health Service persisted during 1958 Though the number of prescriptions dispensed fell from 228 million in 1957 to 224 million in 1958, their total cost rose from £68 million to £73 million and the average cost per prescripton from 5*s* 11½*d* to 6*s* 6½*d* A growing proportion of these prescriptions were proprietary preparations (51% in 1958, as against 47% in 1957 and 37% in 1955) Proprietary preparations also accounted for a growing proportion of the cost of ingredients (72% in 1958, 70% in 1957, and 65% in 1955) Most of them, according to the classification of the Cohen Committee, are not therapeutically superior to standard preparations

As their estimated cost to the N H S was £30 million in 1958–59 (as against £20 million in 1955–56) the Comptroller, not unnaturally, was interested to have news of the voluntary price regulation scheme introduced in June, 1957, for a trial period of three years The Ministry of Health had estimated that the scheme would save the Exchequer up to £750,000 on an annual expenditure of £20 million. In fact, on an annual expenditure of £28 million the scheme had only saved £412,000 One of the chief reasons for this was that ten drugs which had been expected to show price reductions of 25%–40% had in fact qualified for the export price criterion and no reduction had been obtained. According to the published accounts of 43 pharmaceutical firms for 1951–53 their percentages of profits had been above those of general industry and had lately tended to increase whereas the rate for general industry fell The profit rates of the British subsidiaries of American concerns had consistently been much higher than those of general industry The Comptroller freely admitted that these figures showed only very general trends and that many of the firms had important interests unconnected with the N H S But he had noticed that a firm (whose profit in 1957 apparently exceeded 100%) in producing a proprietary drug on which the N H S spent a large sum paid a substantial royalty on any crude material not bought from its American parent. The Comptroller was interested to note that more than half the N H S expenditure on proprietary preparations was on the products of firms which achieved only 3 2% savings under the voluntary price regulation scheme Because of the proportion of drugs excluded from price control and the industry's high rate of profits he doubts the efficacy of the scheme The Ministry, however, believe that the scheme had imposed " some restraint on prices and led to some reductions "

TRAINING IN GENERAL PRACTICE

An experiment in training for general practice, financed partly by the Nuffield Provincial Hospitals Trust, is taking place in Winchester A graduate intending to enter general practice holds a supernumerary appointment, paid at registrar rates, in hospital for one year, during which he obtains experience in various special departments according to his needs, including a six-month appointment in obstetrics and gynæcology, if he has not already held such a post. For the second year he is attached to a general practitioner, under the general-practitioner training scheme, to gain experience of aspects of medical practice other than his own. He is also introduced to the local-authority medical services The object is to produce a general practitioner thoroughly versed in the many aspects of modern general practice, and to study methods of achieving this end

The first appointment was made in Winchester last August and further appointments will shortly be made in Southampton and Portsmouth Another hospital appointment will be available in Winchester in August, 1960, when the present holder moves into general practice under the scheme An advertisement appears in this issue

LADY EWING MEMORIAL

The work of the late Lady Ewing in the cause of the education of deaf children won worldwide renown, and the high reputation of the department of education of the deaf at Manchester University sprang largely from her remarkable skill as a teacher Her friends and former students now feel that this recognition should take a more permanent form and that some suitable memorial to her life and work should be established. They believe that many people, especially those whom she helped directly and indirectly, would be glad to contribute to the cost of its foundation. It has accordingly been decided to establish a research scholarship to be known as the Irene Ewing Research Scholarship Contributions should be addressed to Mr F W Cockersole, 80, Wellington Road, Edgbaston, Birmingham, 15 Cheques should be made payable to the Lady Ewing Memorial Fund

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University of London

Dr E B Chain, professor of biochemistry at the Istituto Superiore di Sanita, Rome, and scientific director of the International Research Centre and head of the biochemistry department, has been appointed to the university chair of biochemistry at the Imperial College of Science and Technology from Oct. 1, 1961 Professor Chain was awarded in 1945 a Nobel prize for medicine jointly with the late Sir Alexander Fleming and Sir Howard Florey for their work on penicillin

The Isaac Wolfson Foundation has given the college £350,000 to build and equip laboratories for biochemistry and chemical microbiology in Professor Chain's department and for the support of teaching and research The equipment of the Wolfson Laboratory will include fermentation units of comparatively large size and workshops for advanced mechanical and electronic equipment It will provide accommodation for training and research in the borderland between biochemistry and chemical engineering, and for research on the biochemical production of chemicals

Mr Kenneth McLay has been appointed reader in otology at the Institute of Laryngology and Otology

University of Edinburgh

Dr E S Blackadder has been appointed part-time lecturer in the general-practice teaching unit and Dr R F Robertson member of the clinical teaching staff in the department of medicine

University of Birmingham

The following appointments have been made

Sir Arthur Thomson, senior fellow in medical history, Dr R F Fletcher, lecturer in the department of medicine, Dr J D Blainey, part-time lecturer in the department of experimental pathology (metabolic diseases), Mr J A Williams, lecturer in the department of surgery

University of Exeter

On May 4 the honorary degree of LL D will be conferred on Dr C J Fuller

Royal College of Obstetricians and Gynæcologists

At the meeting of council on Jan 30, with the president in the chair, the following candidates were elected to the membership

Armaity Aspandiar Anklesaria, Alison M Armstrong, M P Awon, Amarendra Banerjee, J D Begg, Kwesi Kobea Ogye Bentsi-Enchill, K G Bland, Kathleen A S Brosnan G R. Brown, Solomon Burgin, Biman Kumar Chakrabarti, Supriya Chakravorty, F R Clark, Harry Cohen, J B Comerford, F G Cox, Gerda J Crow, M M De La Harpe, R. A Don, Sheila L B Duncan Solomon Ende, P H Foote, A C Fraser, K E Free, I K Furler, W T Gallagher, Susan George, Ronald Giles, C S Hanson, P D Hill Uriah Jacobson Snehalata Bhujanga Kamath, Pun Shui Kan, Swadesh Kataria, Brendan Keane, Bhabesh Chandra Lahiri, Ariffin Bin Ngah Marzuki, Tanendra Nath Mitra T Khoon Fong Ng, D B Paintin, Heather M Panton, Mary C W Paterson E C Pixley, G L S Rankin, L. J Schewitz, S C Simmons, Nargese Jehangir Talati, E P W Tatford, Molly E. Towell, Mary M. Tyndall, R. J Venn, N F Walker, W A W Walters, D K. Williams, L H Wright

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[1] Civil Appropriation Accounts (Classes I-V), 1958-59 H M Stationery Office 1960 Pp 349 19*s*

Royal College of Physicians of London

At the comitia on Jan 28, with Sir Robert Platt, the president, in the chair, the following, having satisfied the censors' board, were elected to the membership

G M Ardran, M D Lpool, John Bamforth, M B Cantab , M A Barraclough, M B Lond , J R Billinghurst, B M Oxon , E J M Bowlby, M D Cantab , D E Christian, M B Lond , G W A Dick, M D Edin , P M S Gillam, M B Cantab , Maurice Gross, M B Lond , D D Guttman, B M Oxon , R M McCredie, M B Sydney, William MacKenzie, M D Lond , A B Myles, M B Cantab , K A K North, M B N Z , H L Nossel, M B Cape Town, E D O Callaghan, M B Queensland, P T Pickens, B M Oxon , Mohamed Sadek Sabour, M B Ain Shams, N L Schwartz, M B W'srand, P J Scott, M B N Z , R S J Simpson, M B Queensland, J H Stewart, M B N Z , Weland Dinnis Stone, B M Oxon , Vetherednam Thuraisingham, M B Malaya, W E Watson, M B Lond

Licences to practise were conferred on the following candidates who had passed the final examination of the Conjoint Board

J H Ainsworth, E G Anderson, R B Andrews, R I A A Aubee, J K Bandoh, Sheila A Beningfield, C A C Bennett, R P Bishop, P G H J Bosley, Margaret Bown, Isobel J N Bradbury, J S Brewer, M G Brook, Diana C Brown, J P B Budgen, R G Bury, Janet R Carruthers, M E Carruthers, Francis Carter, Margaret E Cash, Anne J Cawthorne, M J Chamberlain, Glen Champion, M J S Coe, Bertha C A Coker, T J Colbridge, G P Coleman, Heather J Collins, D H Coombe, A S Cooper, Linda F Courtier, C S D Crane, T W Darling, Faram Dastur, H R Davies, J G Deller, E R Dixon, M W O Dunwoody, Kathleen J B Edwards, Ekpo Ita Efiong, Mary Ellis, M D Farrar, J T L C Fernando, A E Finnigan, D J Fishlock, P R Goddard, A B Griffiths, J B Gritton, J H Hackwood, Edna Hallam, D R Harvey, I B Hayter, Ann Henley, Pauline B Hird, K E F Hobbs, R C Hodge, G T Hollingworth, A S Horner, Peter Howard, E G Hoyen-Chung, K E E Hubble, M K G Hudson, W F G Hulley, M J Hunter, R -K R Innes, Peter Jackson, C W Jamieson, Rosemary Khin Zaw, R S Kirk, Elizabeth S Kitchin, C C Korvin, A P Lees, Eva Lester, Chooi Cheah Lim, J D Lloyd-Still, S J McDonald, Stuart McHardy-Young, Marion MacLellan, Margaret R McMinn, Margaret M McNamara, J J M Marot, June E Marrable, Harriet M C Mason, Pamela J Massie, R E May, R D G Milner, R L Mitchell, Michael Modell, M A Modelski, J F Moore, T S Morley, A E Morris, M D R Morris, J F Murray, A J H Nix, J R Norman, George Nuki, D Ajuebitsi Ogbe, P M Olley, E G J Olsen, S M Patient, H G Peters, J B Phillips, Douglas Pickering, C I Porter, A R C Ralph, Durgapursad Ramprotal, L M Razavi, R J Rew, D A Reynolds, M T Reynolds, Janet Riddle, A D Rogers, P J Y Scott, Paul Sharpstone, C M Signy, G M Slade, J K Smallshaw, M J Smith, Akanni Olufemi Olakunle Sorungbe, F B Stephenson, Mary Stewart, A E Stocks, Norma A Taylor, R G N Thomson, Reginald Tiru-Chelvam, P M J Tombleson, Madueke Ugwunze, Keith Urwin, P L H Vernon, B A Waldron, Judith G Walker, B A Wallace, P J Watt, Tessa Westcott, Myra Wharf, W F White, R W Wille, D E Williams, J G Williams, Norman Williamson, J G Wingfield, Manmohan Singh Wirk, J D Wonham, Adeline Chung Ling Yen

The following diplomas and those mentioned in our issue of Jan 23 (p 234), were conferred jointly with the Royal College of Surgeons

D A —George Chasapakis
D C H —Rabindra Nath Mukerjee
D I H —Fredoon Kaikhushro Amroliwalla, J C Cape, Jitendra Chandra Chakrabarti, Catherine J S Gauvain, P A Lee, Zivojin Lukic, I A McIntosh, Vlasta Mucic, J H Neal, Akhouri Ram Nandan Prasad, R C Robb, E R Simpson, Rosemary Trewby
D P M —A K M N Chowdbury
D T M & H —T W Brown, D H Cook, Ahmad Hadjian, Tanvir Islam, Ashok Dwarkanath Laud, Lyn W Padgett, Robert Scott, Vafiuddin Shaikh, G R Thompson

Royal Society

At a meeting of this society to be held on Feb 11 at 4 30 P M at Burlington House, Piccadilly, London, W 1, Dr Elsie Widdowson, Prof R A McCance, and Mr J W T Dickerson will read papers on some effects of accelerating growth

Medical Research Council

Fellowships in Clinical Research —The Council invite applications for a further series of fellowships in clinical research, tenable at centres in the United Kingdom during 1960–61 These fellowships are open to suitably qualified medical graduates who wish to prepare for a career in clinical research

Further particulars and forms of application may be obtained from the secretary of the Council, 38 Old Queen Street, London, S W 1, with whom applications must be lodged by March 15

College of General Practitioners

Last April the North-West England faculty of the college held in Manchester a symposium on Coronary Disease in General Practice Over 750 doctors applied to attend, and the success of the venture has decided the faculty to hold another similar symposium this year It will be at the Midland Hotel, Manchester, on Sunday, April 10, with Lord Cohen of Birkenhead as chairman This year's subject is Chronic Bronchitis in General Practice

British Medical Association

Sir George Pickering has been nominated as president of the Association for the year 1963–64

Imperial Cancer Research Fund

Lord Salisbury has succeeded the late Lord Halifax as president of this Fund

Scientific Attaché in Soviet Russia

Dr D A Senior, a senior principal scientific officer on the staff of the Department of Scientific and Industrial Research, has been appointed scientific attaché to the British Embassy in Moscow His assignment covers the physical sciences, biology, medicine, and agriculture

Glasgow Royal Mental Hospital

A two-storeyed extension to this hospital at Gartnavel has recently been completed It has cost £100,000 and has 80 beds arranged in 32 single rooms and 8 six-bed dormitories On each floor there is a day-room, a quiet room for reading and writing, and a dining-room Treatment rooms, consulting rooms, and a waiting-room for visitors are also included

Nutrition and the Elderly

The Nutrition Society will hold a symposium on this subject at St Bartholomew's Hospital Medical College, London, E C 1, at 9 45 A M on Saturday, March 19 The speakers will include Prof K J Franklin, Dr C A Boucher, Dr E Woodford-Williams, Dr Alex Comfort, Dr B E C Nordin, Dr C J Earl, and Dr J V G A Durnin Further particulars may be had from Miss D F Hollingsworth, Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, S W 1

Training of Mental Health Staff

The Minister of Health has sought the advice of his Standing Mental Health Advisory Committee on the training required by the staff of centres provided by local health and hospital authorities for the occupation or training of mentally subnormal persons, and the Committee has appointed a subcommittee to consider this The members include Dr J A Scott (chairman), Dr D H H Thomas, Dr J S Hamilton. The secretary is Mr A G Rose, Ministry of Health, Savile Row, London, W 1

The Biochemical Society will hold a symposium on the biochemistry of mucopolysaccharides, on Saturday, Feb 13, at 10 A.M , at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W C 2

Appointments

BOYD, MARY M M , M D Edin , PH D Lond , M SC. N Z , M R C.P , D C.H , D P H , D OBST senior M O (maternal and child welfare), Cornwall

FORREST, A D , M D St And , M R C.P , D P M consultant psychiatrist, Royal Edinburgh Hospital for Mental and Nervous Disorders

FOSTER, GILLIAN M , M B Leeds assistant M O and school M O , West Riding of Yorkshire (Colne Valley division)

GALLOWAY, T McL , M B Edin , F R C.P E , D P H M O.H and principal school M O , West Sussex

McDONALD, ROBERT, M B Aberd , D P H , D P M consultant psychiatrist and physician superintendent, Menston Hospital, Ilkley, Yorkshire

NEAL, F E , M B Sheff , F F R , D M R T consultant radiotherapist, Sheffield National Centre for Radiotherapy and hospital clinics, Sheffield clinical area

SARKANY, IMRICH, M R.C P assistant physician (part time consultant dermatologist), Royal Free Hospital group

SPELLMAN, ANTHONY M B Lond , D P M consultant in psychiatry, Stanley Royd Hospital, Wakefield

STEWART, K A , M B Belf , F F A R C.S , D A part time consultant anaesthetist, General Hospital and Royal Infirmary, Leicester

Birmingham Regional Hospital Board

CASHMORE, P C , M B Lond senior casualty officer (S H.M.O), Burton on Trent group of hospitals

GRIFFITHS, PETER M.B , B SC Wales, D O part-time consultant ophthalmologist, Burton on Trent group of hospitals

ROITH, A I , L.R.C P I , D C H , D P M consultant psychiatrist and deputy medical superintendent, Monyhull Hall, Birmingham

Births, Marriages, and Deaths

BIRTHS

GELLMAN —On Jan 22, at the Winnipeg General Hospital to Dr and Mrs D D Gellman (formerly Dr Vera Armett) of Ste 307, 81, Roslyn Road, Winnipeg—a son, Andrew John

The Lancet · Saturday 13 February 1960

IMMEDIATE TREATMENT OF CEREBRAL INFARCTION

SEVEN YEARS' PERSONAL EXPERIENCE

A. Barham Carter
M.A., M.D. Cantab, M.R.C.P., D.P.M.
PHYSICIAN, ASHFORD HOSPITAL, MIDDLESEX

Recent years have seen a revival of interest in the treatment of cerebral infarction, and some increase in knowledge of its ætiology, pathology, and mechanics Formerly treatment had three main objects—preservation of life, prevention of nursing disasters, and rehabilitation of the disabled patient. No real attempt to influence the occlusion or its effect on the brain was made until Leriche and Fontaine (1934) suggested that stellate-ganglion block might improve the blood-supply of the infarcted brain and lessen the hemiplegia, even in longstanding cases Since then this and other methods, which may involve the use of powerful and dangerous drugs, have been widely studied and employed, but the position is still far from clear, and medical opinion is sharply divided on the dangers and results of treatment

In view of this it was decided to study all patients below the age of 80 with cerebral infarction admitted to Ashford Hospital in the 7-year period from January, 1952, to December, 1958 Owing to the generosity of my colleagues this has been a personal series, and some of these cases have already been reported (Carter 1957, 1959)

Definition and Ætiology

Cerebral infarction is here defined as an ischæmic condition of the brain, producing a persistent focal neurological deficit in the distribution of one of the major cerebral arteries Consciousness may or may not be lost, there may be an obvious embolic source, and there should be no evidence of cerebral contusion, abscess, or hæmatoma. The cerebrospinal fluid (C.S.F.) is almost always normal to the naked eye.

For many years this condition was attributed to cerebral embolism or to cerebral thrombosis, depending on the speed of onset of symptoms and the presence or absence of an embolic source. But even this diagnosis was inferential, and what seemed a classical embolism could not always be substantiated as such at necropsy It now appears that other conditions may produce cerebral infarction.

First, in many patients it has been impossible to demonstrate any clot either on arteriography (Livingston et al. 1955) or at necropsy (Hicks and Warren 1951), though later work suggests that some small proven thrombotic lesions escape arteriographic diagnosis (Alajouanine 1957), and that at necropsy small clots are often destroyed if the brain is cut while soft (Adams 1958) Therefore to say that clotting has not occurred because no clot has been found is probably unjustifiable.

Second, considerable attention has been focused on the internal-carotid and vertebral arteries in the neck, and the effects of arterial occlusion have been extensively studied (see Symonds [1957] and Hutchinson and Yates [1957]) There seems no doubt that arterial occlusion in the neck may produce cerebral infarction without a cerebral clot.

Third, cerebral arteriosclerosis has been shown to produce a state of general cerebrovascular insufficiency which may proceed to selective ischæmia or infarction by reason of focal arterial narrowing combined with systemic hypotension (Hausman 1958) Meyer and Denny-Brown (1957) showed that in monkeys collateral circulation of the brain is at first opened up by lowering of intraluminal pressure, but when the pressure falls below the critical level of 50 mm. Hg the whole system collapses and a reversible ischæmic cerebral anoxia is converted without thrombosis or embolism to irreversible infarction. But Adams (1958) regards this as an uncommon cause of major cerebral infarction, often accepted too easily at necropsy He suggests that, if the arterial tree from aorta to the site of infarction is examined carefully, and if search is made assiduously for sources of embolism, some evidence of thrombotic occlusion of the vessel supplying the infarct will be found in the vast majority of cases

The Series

One thousand and two patients below the age of 80 were admitted to Ashford Hospital with the clinical diagnosis of "stroke" between 1952 and 1958 inclusive (table I) Of these, five hundred and ten, who were thought to have cerebral infarction, form the subject of the present inquiry The figures seem very consistent from year to year, and show that cerebral infarction accounted for just over half and cerebral embolism for less than a tenth of all "strokes"

TABLE I—CASES OF "STROKE" ADMITTED TO ASHFORD HOSPITAL, SHOWING SEX AND ÆTIOLOGY

Year	No of cases	Sex		Ætiology		
		Males	Females	Embolism	Thrombosis	Hæmorrhage
1952	140	70	70	16	54	70
1953	154	75	79	18	62	74
1954	134	59	75	15	47	72
1955	140	65	75	9	61	70
1956	140	67	73	9	63	68
1957	147	70	77	10	66	71
1958	147	72	75	8	72	67
Total	1002	478	524	85	425	492

American figures (Murphy 1954) suggest that thrombosis accounts for 65%, embolism for 5%, and hæmorrhage (including subarachnoid hæmorrhage) for 30% of all strokes. Glynn's figures (1956) accord more closely with mine. Reviewing the consecutive cases of cerebrovascular disease admitted to a London general hospital during 4 years, he found that 56% had cerebral thrombosis, 36% had hæmorrhage, 3% had embolism, and 5% were undiagnosed.

Distribution and Type of Infarction

In the eighty-five cases of cerebral embolism the diagnosis was made on the very sudden appearance (often within seconds) of hemiplegia, hemianopia, or aphasia in the presence of auricular fibrillation, subacute bacterial endocarditis, recent coronary thrombosis, or mitral stenosis with sinus rhythm

Such patients may, of course, have other cerebral disorders producing neurological deficit, but when a very sudden unilateral cerebral lesion develops during the waking hours

TABLE II—CASES OF CEREBRAL EMBOLISM

Year	No of cases	Sex		Average age (yr)	Hemiplegia		
		Males	Females		Right	Left	None
1952	16	5	11	52	5	10	1
1953	18	7	11	50	6	10	2
1954	15	5	10	48	5	8	2
1955	9	4	5	53	4	5	
1956	9	4	5	56	4	4	1
1957	10	4	6	57	5	4	1
1958	8	3	5	55	3	4	1
Total	85	32	53	53	32	45	8

TABLE III—ÆTIOLOGY OF CEREBRAL EMBOLISM

Year	No of cases	Ætiology					
		Mitral stenosis + fibrillation	Mitral stenosis	Fibrillation	Cardiac infarct	Sub-acute bacterial endocarditis	Thyrotoxicosis + fibrillation
1952	16	8	1	2	2	2	1
1953	18	10	2	2	2	1	1
1954	15	7	1	2	4	0	1
1955	9	4	1	0	3	0	1
1956	9	5	0	0	4	0	0
1957	10	3	0	0	6	1	0
1958	8	2	0	1	5	0	0
Total	85	39	5	7	26	4	4

in a patient with a known source of potential emboli, the diagnosis of cerebral embolism seems reasonable A lumbar puncture was done in every case in an attempt to exclude a hæmorrhagic lesion

All the cases of cerebral embolism are analysed in table II, which shows that since 1954 the incidence has decreased Table III shows that the ætiology has changed also, with cardiac infarction tending to replace mitral stenosis as the commonest underlying heart lesion The distribution of infarction in the eighty-five patients with cerebral embolism was mid-cerebral in seventy-seven (thirty-two with right hemiplegia, and forty-five with left hemiplegia), posterior-cerebral in four, anterior-cerebral in one, and vertebral-basilar in three

In the four hundred and twenty-five patients with cerebral infarction not obviously due to embolism the diagnosis was based on a persistent focal neurological disorder in the distribution of one of the major cerebral arteries, in the absence of a history of head injury, and with C S F normal to the naked eye In addition there was no clinical evidence of tumour, abscess, or hæmorrhage

A differential diagnosis between cerebral thrombosis, carotid or vertebral stenosis or thrombosis, and cerebral ischæmia with atheroma but without thrombosis is often impossible clinically, because carotid occlusion may equally produce either no disability at all, or attacks of transient cerebral ischæmia before infarction, or a classical complete "mid-cerebral type" infarction without warning Similarly the infarction due to tissue anoxia associated with narrowed vessels often cannot be distinguished clinically from that due to thrombotic occlusion.

To obtain some idea of the relative frequency of the three main types of cerebral infarction either arteriography during life or necropsy is necessary In this series I thought that routine carotid arteriography was unjustifiable, in view of its possible dangers, and particularly the general cerebral vasoconstriction often produced after puncture of the carotid and injection of the dye However, when there was doubt about the diagnosis either on admission or during the course of the illness, arteriography was performed the condition of two of the forty-five patients subjected to this investigation became worse Of these doubtful cases twenty-seven were found to have carotid occlusion, but many more of the whole series must have had stenosis or occlusion of the carotid or vertebral arteries

Occasionally the diagnosis was made on the history of ipsilateral recurrent visual loss with attacks of contralateral weakness affecting the arm mostly, or on the finding of a systolic murmur over the carotid opposite the C6 vertebra The pulse over the affected carotid was rarely diminished In fifty-two cases (from 1954 to 1958) a full postmortem examination of the cervical vessels was made in addition to the usual brain examination, twenty-two showed infarction with atheroma and without thrombosis, twenty had thrombus in the vessel supplying the infarcted area, and ten had cervical-carotid occlusion (complete in seven, and incomplete in three) If morbidity is proportional to mortality it seems that carotid occlusion may account for 20% of cases of cerebral infarction

The meaning of the terms used must be strictly defined and agreed "Cerebral thrombosis" has become so much a part of current medical terminology that it should, perhaps, still be used for patients with cerebral infarction, though there may be no clot and the occluding lesion may not even be cerebral. "Cerebral infarction", another possible term, is correct, but has the disadvantage of including patients with cerebral embolism The term "cerebral thromboembolism" is accepted in North America "Non-embolic cerebral infarction" (Carter 1959) is clumsy and not always correct, because a cerebral thrombus may occasionally produce subsequent infarction by distal embolism Thus it may be as well to retain "cerebral thrombosis" as the provisional descriptive term for cerebral infarction not obviously due to embolism, and to make a more accurate final diagnosis when the appropriate investigations are completed

Describing the onset and course of cerebral infarction is equally difficult For the gradual type the following terms are in current use "slow-onset stroke", "ingravescent infarction", "ingravescent stroke", and "stroke-in-evolution" (Fisher 1958) The word "stroke" has caused much confusion because it is sometimes used for the neurological deficit, sometimes for the state of consciousness, and sometimes for the first symptoms of brain damage Moreover it may include all types of lesion from a hypertensive cerebral crisis, through embolism and thrombosis, to any sort of intracranial hæmorrhage Because of this confusion it would be wise to banish the word from medical terminology, as we have banished "heart attack" "Ingravescent cerebral infarction" could then be used, being defined as cerebral infarction in which the neurological deficit has not yet become absolute, and in which the onset of symptoms takes time to develop The exact time is not of great importance therapeutically, though arbitrarily over 2 hours is considered slow, and under 2 hours sudden, because in most patients the time falls well to one side of this line (Carter 1959)

TABLE IV—CASES OF NON-EMBOLIC CEREBRAL INFARCTION (CEREBRAL THROMBOSIS) SHOWING AGE, SEX, AND TYPE OF OCCLUSION

Year	No of cases	Sex		Average age (yr)	Type of occlusion		
		Males	Females		Anterior-cerebral	Mid-cerebral	Vertebral-basilar
1952	54	24	30	62	0	51	3
1953	62	30	32	65	0	56	6
1954	47	23	24	64	1	40	6
1955	61	30	31	65	1	52	8
1956	63	30	33	67	0	53	10
1957	66	34	32	64	1	56	9
1958	72	34	38	66	0	62	10
Total	425	205	220	65	3	370	52

Cerebral infarction was commonly distributed in the territory of the mid-cerebral artery, of the four hundred and twenty-five infarctions three hundred and seventy were in this group Of the other infarcts, forty were in the vertebral-basilar territory, seven patients had posterior-inferior-cerebellar-artery occlusions, five had posterior-cerebral occlusions, and three were anterior-cerebral (see table IV)

Differential Diagnosis

The most important differential diagnosis of cerebral infarction is from cerebral hæmatoma, especially when the question of anticoagulant therapy is considered

Subdural hæmatoma is less difficult to differentiate than intracerebral hæmatoma as a history of injury or fall, or fluctuation of signs—often with pupillary changes—may be helpful Some loss of consciousness is common, and the neurological deficit spreads smoothly rather than irregularly, showing greater fluctuation than arises with infarction Six patients of the present series were proved by carotid arteriography to have subdural hæmatoma, and three to have intracerebral hæmatoma

TABLE V—RESULTS OF TREATMENT IN CEREBRAL EMBOLISM (ONE CASE FROM 1957 AND ONE FROM 1958 ARE NOT INCLUDED)

Year	No of cases	Recovered	Improved	Not improved	Died	Treatment
1952	16	4	1	2	9	Repeated stellate block
1953	18	4	2	3	9	No treatment
1954	15	8	3	0	4	Single stellate block and anticoagulants
1955	9	5	1	1	2	Anticoagulants
1956	9	4	2	1	2	
1957	9	4	2	1	2	
1958	7	3	1	2	1	

Difficulty arises more often with primary intracerebral hæmatoma. This condition is easy to recognise in about 60% of cases, because the patient has a sudden attack with loss of consciousness, and the C.S.F is bloody or xanthochromic. Hypertension is commonly severe, and, if the patient improves, headache and vomiting are prominent. Improvement is followed by further decline, with signs of cerebral compression, which if unrelieved leads to death. In some patients, however, the history and course is much more like cerebral infarction, and then the clinical diagnosis becomes difficult (Elkington 1958, Kelly 1958) Anticoagulants are likely to be used for the type of infarction with a quiet ingravescent onset and little loss of consciousness, the course of which is characterised by a step-like pattern of motor or sensory loss, with sudden increase or spread of weakness to previously unaffected areas Headache is not prominent, some recovery follows within a few days, and signs of cerebral compression are absent. The patient is usually normotensive, the C.S F is clear, and the neurological deficit is in the distribution of one of the major cerebral arteries Unfortunately some of these features have been found in primary intracerebral hæmatomata. McKissock et al. (1959) have published their experiences with two hundred and forty-four consecutive cases of this condition, proved either at operation or necropsy They found that in 11% the onset was gradual, in 20% the C.S F was clear, in 23% the blood-pressure was normal, and in 46% consciousness was preserved They also found that the accuracy of arteriography in diagnosis was below 70%

In the present series little difficulty was found in diagnosing cerebral embolism In the case of non-embolic cerebral infarction (suitable for anticoagulant treatment) the diagnosis was accepted if all the criteria of slow onset, step-wise course, normal blood-pressure, clear C S F, involvement of the territory of one cerebral artery, and little loss of consciousness were present.

Treatment

From 1952 to 1955 an attempt was made to assess the value of different forms of treatment, and to balance any benefit against any adverse effects These results, with details of treatment, have already been recorded in full (Carter 1957, 1959)

Briefly, cerebral embolism was considered separately from the other forms of cerebral infarction. In 1952 repeated stellate-ganglion block was used, and the results were compared with an untreated series of patients admitted in 1953 In 1954 the patients were treated by a single stellate block followed by anticoagulant therapy, and the 1955 groups by anticoagulants alone The results (table V) showed that the patients treated by stellate block did not improve, but those treated within a week of onset by anticoagulants with or without one stellate-ganglion block showed significant improvement.

The other forms of cerebral infarction were grouped together as "cerebral thrombosis" In these patients similar methods were used, though the timing was different. In 1952 no specific treatment was given, but in 1953 repeated stellate block was used. In 1954 the inhalation of 5% carbon dioxide in oxygen through a B L.B mask was employed for 5 minutes every hour during the first 48 hours, as this is said to produce the greatest cerebral vasodilatation with increased blood-flow (Kety and Schmidt 1948) In 1955 all patients were treated by anticoagulants in the form of heparin by injection combined with oral phenindione ('Dindevan') The results (table VI) showed that repeated stellate block produced no improvement, that carbon dioxide produced slight improvement, and that anticoagulants produced still more improvement. This became significant ($P < 0.05$) when the cerebral infarction was of slow onset and incomplete.

TABLE VI—RESULTS IN CEREBRAL THROMBOSIS CASES UNSELECTED

Year	No of cases	Recovered	Improved	Not improved	Died	Treatment
1952	54	13	12	9	20	No treatment
1953	62	14	16	8	24	Stellate block
1954	47	15	12	4	16	CO_2 inhalation
1955	61	20	16	9	16	Anticoagulants

After this experience, certain modifications were instituted during 1956–58 Stellate-ganglion block and carbon-dioxide therapy had not been of value in the treatment of cerebral infarction, and with two exceptions (cerebral embolism, and particularly ingravescent cerebral thrombosis if the paralysis was not complete) this was also true of anticoagulants

The modifications that seemed necessary were three

1 The age-limit of 80 was lowered to 70 (though occasional exceptions in the case of "young" septuagenarians were allowed) because visceral bleeding was more common in old people even with prothrombin-times only twice normal, and because of the greater difficulty in prothrombin-time control in this age-group

2 The dose of anticoagulants was reduced. In the previous years, when full doses were given to raise the prothrombin-time to four times normal, bleeding often occurred in the patients over 60, but a smaller dose seemed to produce equally good results The following method was used for all patients (a) on admission heparin 12,500 units was given intravenously with phenindione 200 mg orally, (b) two similar doses of heparin were given intramuscularly 6 and 12 hours after admission, and (c) during the second 24 hours phenindione 150 mg was given in divided doses, and thereafter sufficient to keep the prothrombin-time between two and three times normal.

3 The third modification was to prolong the treatment from 2 to 4 weeks Originally 2 weeks' treatment was considered adequate, as in thromboembolism of the limb vessels, but an occasional return of symptoms in the 3rd week suggested that this was not long enough for cerebral infarction. Therefore a full 3-week course was given, followed by a 4th week of gradually reduced dosage so that the prothrombin-time did not fall too quickly

The results during 1952–55 had provided some indications for the treatment of cerebral infarction. Anti-

TABLE VII—CEREBRAL THROMBOSIS RESULTS OF TREATMENT IN SELECTED INGRAVESCENT CASES

Year	Total no of cases	Anticoagulant treatment					No anticoagulant treatment				
		No of cases	Recovery	Improvement	No improvement	Death	No of cases	Recovery	Improvement	No improvement	Death
1956	24	12	6	3	2	1	12	4	2	3	3
1957	20	10	5	3	1	1	10	4	2	2	2
1958	22	11	6	2	2	1	11	4	2	3	2
Total	66	33	17	8	5	3	33	12	6	8	7

TABLE VIII—RESULTS OF CONTROLLED TRIAL IN CEREBRAL THROMBOSIS OF SLOW ONSET, SHOWING IMPROVEMENT WITH TREATMENT IF LESION IS INCOMPLETE

Year	No. of cases	Anticoagulants				No anticoagulants			
		Lesion incomplete		Lesion complete		Lesion incomplete		Lesion complete	
		Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died
1956	24	6	2	3	1	4	3	2	3
1957	20	5	1	3	1	2	2	3	3
1958	22	5	1	3	2	3	4	3	1
Total	66	16	4	9	4	9	9	8	7

coagulants were most useful in cerebral embolism, and less so in certain types of cerebral thrombosis. Early treatment was reviewed and modified. During 1956–58 all patients with cerebral embolism were treated with anticoagulants unless there was blood in the C.S.F., unless they were over 70, and unless their diastolic blood-pressure was over 120 mm. Hg. Only two patients were rejected on these grounds, and twenty-five admitted in these 3 years were treated with anticoagulants. The results, shown with the previous years' results in table V, are consistent.

The situation was different with cerebral thrombosis because the indications for treatment were not so clear, and the contraindications were more obvious than in overt cerebral embolism. Hence selection of patients for treatment during 1956–58 seemed desirable. Patients with a history of onset of lesion developing within 48 hours and lasting more than 2 hours, with a diastolic pressure below 120, and with no macroscopic evidence of blood in the C.S.F. were selected for study. During these 3 years two hundred and one patients were admitted with the diagnosis of cerebral infarction, without obvious embolic source, and in sixty-six of these the onset was slow, as defined above. They were divided into two equal groups, and alternate patients were treated with anticoagulants. The results are shown in table VII.

Results

Assessment

With few exceptions most of the neurological recovery from cerebral infarction takes place in the first 4 weeks, and very little change, apart from that due to re-education and adaptation, can be expected after 3 months. Certain workers—notably Leriche and Fontaine (1934) in France—have held more optimistic views, but experience in this country is less encouraging. The final assessment was made by examination 6 months after infarction, and the patients were simply divided into four groups: recovered, improved, not improved, or died.

"Recovered" meant that the patients noticed little or no disability and were able to resume successfully their former occupation. Some loss of fine-movement dexterity was considered compatible with recovery if the above criteria were fulfilled. Probably all patients with initial hemiplegia continue to show slight permanent pyramidal signs. "Improved" meant that some useful movement was possible at elbow and wrist, and that the patient could get about with slight assistance. "Not improved" indicated no return of arm movement below the shoulder, though some leg function was regained. Almost all patients who survive infarction with hemiplegia regain some movement of the shoulder and the leg.

Analysis of Results

The results in patients with cerebral embolism are recorded in table V. In 1952–53 the results were good ("recovered" or "improved") in eleven out of thirty-four patients, and this 33% recovery was unchanged by stellate-ganglion block. This compares with the usual recovery-rate of about 40% (Wells 1959). In the following years forty-nine patients were treated with anticoagulants (preceded in 1954 by a single stellate block) and in thirty-three the results were good, representing 66%. These figures are significant (P 0·025), and the proportion of patients who recovered was doubled in the treated group.

The results in patients with cerebral thrombosis were rather harder to assess (table VI). The natural history suggests that just about half the patients recover, about a third die within a year, and the remaining sixth are unimproved. With carbon-dioxide therapy a slight improvement in these figures was obtained, and with anticoagulant therapy further slight improvement occurred so that 60% showed fairly good recovery.

The usual prognostic factors, studied in all the groups, were equally distributed. It soon became apparent that old age, severe and extensive infarction, prolonged unconsciousness, delay in admission to hospital resulting in dehydration and bedsores, severe hypertension, and a history of previous strokes were all bad signs. The patient most likely to die was the neglected old man in poor condition with signs of longstanding ischæmic heart-disease. Lesions of slow onset carried an overall better prognosis than those of rapid onset, and this improvement could be bettered by anticoagulants, particularly if the lesion had not become complete by the time treatment was begun.

The results in the patients selected along the above lines during 1956–58 are shown in table VII. If the "recovered" and "improved" groups are taken together, as opposed to those who died or did not improve, it will be seen that twenty-five of the thirty-three patients who were treated did well as opposed to eighteen of the thirty-three who were untreated. This is 75% against 54%, and represents a just significant improvement (P 0·05).

If the patients are selected further according to the completeness or not of the lesion when treatment was begun (table VIII), greater improvement can be seen. The recovery-rate in the treated "incomplete" group was 80%, and in the treated "complete" group 69%. In the untreated incomplete group the recovery-rate was 50% and in the untreated complete group 53%. This improvement from 50 to 80% is significant ($P < 0·05$), suggesting that the best results will be in the patient whose lesion is slowly getting worse.

Discussion

The results of this investigation suggest that the only specific treatment likely to help patients with cerebral infarction is anticoagulant treatment. This has been shown to be of some value for patients with recent cerebral embolism, or with infarction of slow onset, although further selection of patients is necessary in terms of hypertension, appearance of the C.S.F., and age. Experience has also shown that the indications have become fewer and the criteria for treatment more stringent

Mechanism of Treatment

The mechanism of anticoagulant treatment once cerebral infarction has taken place is not completely understood, but the benefit must arise in one or more of three ways Spread or propagation of clot (which sometimes occurs both distally and centrally from the original thrombosis) may be prevented, and, since this spread often involves anastomotic vessels, anticoagulants may keep the infarcted area from enlarging They may also prevent initial clot formation if the infarction were caused by atheromatous narrowing without thrombosis, combined with systemic hypotension, and they may prevent distal embolism in the case of thrombosis of large vessels This seems to be particularly useful in infarction associated with carotid and vertebral stenosis (Symonds 1957) Indeed one is tempted to suppose that the stepwise progress of ingravescent cerebral infarction is produced by repeated distal embolism, thus accounting for the curious paradox in this report—namely, that the most acute infarct from cerebral embolism and the most chronic from ingravescent cerebral ischæmia are the only types helped by anticoagulants If this is so then the comparative freedom from local hæmorrhage in this series may be put down to the fact that clinical embolism often affects healthy arteries, and distal embolism affects the smaller cerebral arteries which are known to escape atheroma Conversely, in sudden lesions due to cerebral thrombosis the clot is presumably situated at the most unhealthy part of the vessel, and in this type of case anticoagulants have been ineffective and occasionally harmful One must also recognise that apparently adequate prolongation of the prothrombin-time will not always prevent thrombosis, and all physicians experienced in this work have known the mortifying disappointment of seeing a major thrombus strike at this time

Dangers of Treatment

The evident dangers of anticoagulant treatment, which have been rightly emphasised by most authors, are three in number The first is bleeding into and around the infarcted brain, the second is major visceral bleeding producing hypotension, and the third is the risk of treating intracranial hæmatomata with anticoagulants because of errors of diagnosis

Medical opinion is sharply divided on the possibility and extent of bleeding around or into infarcted brain Experimental work suggests that anticoagulants do considerable harm in this way

Sibley et al (1957) showed that experimental hæmorrhagic cerebral infarcts in dogs would bleed further after the administration of dicoumarol, but when the infarcts were anæmic no such tendency was found Moyes et al (1957) showed that infarctions produced in dogs by injecting plastic vinyl acetate into the internal carotid artery were more hæmorrhagic in animals having anticoagulants Similarly Peterman et al. (1959) produced cerebral infarction in dogs by the intracarotid injection of blood-clot. After 3 days about half the animals were given dicoumarol, and at the end of 15 days the infarctions in the treated animals were conspicuously more hæmorrhagic and the mortality was higher

Clinically, however, the evidence against anticoagulants is less strong Fisher (1958) found no evidence that anticoagulants cause hæmorrhage into infarcted brain, and my experience (Carter 1957, 1959) agrees with this

Similarly Wright and McDevitt (1954) found no clinical evidence that anticoagulant treatment was harmful, even in hæmorrhagic cerebral infarction. Brain (1957) thinks it unwise to give anticoagulants within at least 3 weeks of an attack of cerebral infarction, and this view is supported on the Continent by de Morsier and Tissot (1957) Vastola and Frugh (1959) have reported a very disturbing series of fifty-five consecutive patients with recent cerebral infarction treated by anticoagulants There was no control series, but the authors did not think their patients showed improvement as compared with that " expected in a similar group " Twenty of the fifty-five patients bled in various parts of the body, and in four anticoagulants were blamed for extensive brain hæmorrhage—three into the infarct and one elsewhere On the other hand Wells (1959) treated with anticoagulants twenty-nine patients with 34 attacks of cerebral embolism, with results better than in his untreated series and without intracranial bleeding

Two examples will show the danger of attributing cerebral hæmorrhage to anticoagulant therapy in patients who are being treated for cerebral infarction

CASE 1 —A man, aged 67, was admitted in November, 1958, with 3 weeks' history of progressive vertigo, left homonymous hemianopia, and weakness of the legs He had had a transient right hemiparesis 12 months previously, with some personality deterioration. On the day of admission he was found lying on the floor, dazed and stuporose, with left hemiparesis Lumbar puncture showed clear C S.F under normal pressure, containing 9 lymphocytes per c.mm. and 50 mg of protein per 100 ml. Next day the left hemiparesis was deeper and bilateral facial weakness had appeared. Basilar stenosis with possible thrombosis was diagnosed and anticoagulant treatment was begun. All the signs improved except the hemianopia, which remained complete

After discharge the patient was advised to continue anticoagulants (phenindione 50 mg daily), which kept his prothrombin-time steady at about 30 seconds 6 weeks later he complained of violent headache, became rapidly unconscious, and died (the prothrombin-time was then 20 seconds) At necropsy a massive subarachnoid hæmorrhage was found, and anticoagulants were blamed until it was seen that a friable tumour, adherent to the right wing of the sphenoid, had ruptured the cavernous sinus Sections showed that this was a hitherto unsuspected cellular meningioma Basilar stenosis was present, the right posterior-cerebral artery was grossly narrowed, and the right occipital lobe showed recent softening, neither the cerebral nor cervical arteries contained thrombus

CASE 2 —A man, aged 68, was admitted in March, 1959, with an increasing left hemiparesis of 6 hours' duration The left arm was completely paralysed, but weakness of the left leg was moderate He had no sensory loss or hemianopia. His blood-pressure was 180/115, and the C.S F was clear Anticoagulant therapy was begun. His hemiparesis improved, and he was discharged 4 weeks later, using a stick and with movement of all joints in the left arm A month later, when he was readmitted with a return of left-sided weakness, it was decided to use long-term anticoagulant therapy, and he was stabilised on phenindione 75 mg daily 4 months later he was again admitted, now moribund, and with signs of cerebral hæmorrhage This diagnosis was confirmed at necropsy, a large hæmorrhage having destroyed the right cerebral hemisphere. The prothrombin-time of 12 seconds on the day the patient died was disbelieved, until his relatives explained that he had not taken his tablets for at least a month before his death

The second danger of treatment—that of visceral bleeding—seemed at first a major risk, particularly in the elderly In the second half of this series, when the dosage of anticoagulants was reduced, 17 minor hæmorrhagic episodes arose in nine patients Of these hæmaturia accounted for 7, epistaxis for 5, subconjuctival hæmorrhage for 3, and facial bleeding after shaving for the other 2 In only one patient was the prothrombin-time found to be over 40 seconds, and in all the patients treatment was resumed after a 2-day interval Luckily no major visceral bleeding was encountered in the last 3 years died of their injuries or from complicating infection despite carefully controlled conservative treatment and in many cases repeated hæmodialysis

We describe here the natural history of uncomplicated acute tubular necrosis in a selected group of 28 patients in whom the primary cause of the disease was medical or obstetric (table I) All of these patients recovered completely with or without hæmodialysis This selection avoids the difficulties due to the irregular and unpredictable course when the condition is complicated by uncontrolled infection or extensive tissue damage, and permits analysis of the full course of the disease from onset to full recovery The series may be unrepresentative of all examples of uncomplicated acute tubular necrosis, since probably the more severe cases are referred to centres equipped for hæmodialysis This difficulty of sampling is, however, almost universal in descriptions of disease based on the experience of a single hospital 5 patients with proximal tubular necrosis have been included since their course seemed to be identical with that of acute tubular necrosis

During this period deaths in cases diagnosed on admission as uncomplicated acute tubular necrosis numbered 11 (table II) 3 of these patients were proved at necropsy to have renal cortical necrosis with almost complete destruction of all nephrons The fatal cases will be described after the analysis of the 28 patients who recovered

Management

All patients were treated by a standard conservative regime The diet consisted of a 20% solution of lactose by mouth, a volume of X+400 ml daily being given from November to April, and X+500 ml daily from May to October, where X ml is the total volume of the measurable fluid loss from the patient on the previous day When intractable uræmic vomiting occurred, the same volume of sterile 40% glucose was given by infusion, preferably into the superior vena cava, but at times into the inferior vena cava, instead of by mouth Soluble insulin was given by injection when the blood-sugar was over 200 mg per 100 ml Sulphonamides or antibiotics were given only in cases with established infection, but all patients were isolated and standard methods of barrier nursing were used Infusions of packed cells were given in amounts large enough to maintain the hæmoglobin concentration above 10 2 g per litre (70% Haldane) Non-virilising androgens in the dosage recommended by McCracken and Parsons (1958) were given to the female patients during the latter half of the series Blood-urea and plasma potassium and bicarbonate were measured daily, and electrocardiography was performed daily throughout the whole of the oliguric stage Hæmodialysis was carried out by a rotating-drum artificial kidney when any one of the following indications was present (*a*) blood-urea above 400 mg per 100 ml , (*b*) plasma-bicarbonate below 12 mEq per litre, (*c*) plasma-potassium above 7 5 mEq per litre, despite therapy with cation-exchange resins by mouth (Elkinton et al 1950, Evans et al 1953), (*d*) electrocardiographic evidence of intraventricular block with widening of the QRS complexes from hyperkalæmia, (*e*) uræmic stupor, coma, vomiting, hiccough, or fits

Appropriate supplements of sodium and potassium salts were given in the diuretic stage, usually in amounts equal to the urinary losses of the previous day A diet of carbohydrate alone was continued until the blood-urea fell below 100 mg per 100 ml , unless the patient became extremely hungry and demanded solid food

Stages

The course of the disease, as suggested by Bull et al. (1950), has been divided into an onset stage, oliguric stage, early diuretic stage, late diuretic stage, and convalescent stage, but the definitions of the five stages adopted here are more precise and better adapted for clinical use

Onset stage—This is the short period between the acute event causing the renal damage and the development of

TABLE II—FATAL CASES OF ACUTE TUBULAR NECROSIS AND RENAL CORTICAL NECROSIS

Diagnosis and case no	Age (yr)	Sex	Diagnosis	Stage of illness at death	Hæmodialysis	Postmortem findings
Acute tubular necrosis						
1	38	F	Induced abortion at 24 weeks, terminal septicæmia	10th day diuretic phase	+	Multiple hæmorrhagic abscesses (lungs, kidneys, heart, and brain), renal tubular necrosis
2	37	F	Induced septic abortion at 12 weeks, pelvic cellulitis	13th day oliguric phase	–	Purulent pericardial effusion with myocardial abscess, pelvic peritonitis, renal tubular necrosis
3	29	F	Induced septic abortion at 16 weeks, pelvic peritonitis	10th day oliguric phase	+	Ruptured uterus with general peritonitis, renal tubular necrosis
4	23	F	Induced septic abortion at 18 weeks	6th day diuretic phase	+	Renal tubular necrosis, septicæmia with pyodermia
5	75	F	Sensitivity reaction to sulphonamides	14th day oliguric phase	–	Renal tubular necrosis, no evidence of glomerulitis
6	54	M	Overdose of morphine with hypotension, staphylococcal pneumonia	Late diuretic phase—blood-urea 100 mg per 100 ml	– –	Lung abscess with empyema, healed renal tubular necrosis
7	61	M	Pneumonia, hypotension	2nd day oliguric phase	–	Hæmorrhagic pulmonary œdema, no evidence of pneumonia, renal tubular necrosis
8	57	M	Acute tubular necrosis due to pancreatitis	17th day oliguric phase	++	Renal tubular necrosis, hæmorrhagic pancreatitis
Renal cortical necrosis						
9	35	F	Concealed accidental hæmorrhage at 28 weeks, cerebral hæmorrhage	9th day oliguric phase	+	Symmetrical renal cortical necrosis, cerebral hæmorrhage
10	32	F	Concealed accidental hæmorrhage at 32 weeks, staphylococcal septicæmia	19th day early diuretic phase	+	Symmetrical cortical necrosis of kidneys
11	35	F	Concealed accidental hæmorrhage at 27 weeks, septicæmia	18th day oliguric phase	++	Symmetrical renal cortical necrosis

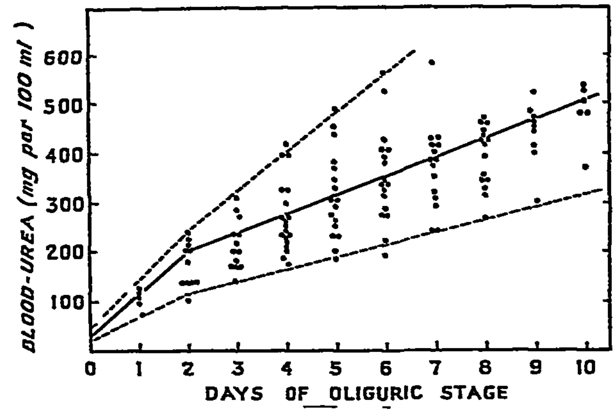

Fig 1—The rise of blood-urea during the oliguric stage of acute tubular necrosis before hæmodialysis or in undialysed patients

The rate of rise of blood-urea is greater in the first two days The regression line is calculated from days 2 to 7 inclusive, as after day 7 many of the higher blood-urea values have been reduced by hæmodialysis

established oliguria with a urine output in an adult patient of less than 400 ml per day

Oliguric stage—This is the interval between the onset stage and the first day when the urine volume is consistently more than 400 ml. per day

Early diuretic stage—This is the period between the end of the oliguric stage and the first day when there is an unequivocal and sustained fall of the blood-urea

Late diuretic stage—This is the period between the end of the early diuretic stage and the first day on which the blood-urea is consistently lower than the upper limit of normal—i e 45 mg per 100 ml

Convalescent stage—This is the period in which, although the blood-urea is normal, the patient is still unable to engage in normal activities or duties

In this account of the clinical course of uncomplicated acute tubular necrosis, the daily urine volume and the values of blood-urea are considered to be the two most important biochemical indices Although concentrations of plasma potassium and bicarbonate are of especial value in assessing the need for hæmodialysis, they may both be influenced by relatively minor therapeutic procedures such as the administration of cation-exchange resins or infusions of sodium lactate Their values do not necessarily therefore reflect the course of the disease In contrast, the blood-urea will rise continuously unless spontaneous diuresis occurs or hæmodialysis is applied

Onset Stage

Since all patients were referred from other hospitals early in the oliguric stage there was unfortunately no opportunity to study the patients in this important stage of the disease

Oliguric Stage

Complete anuria is extremely rare in acute tubular necrosis Urethral catheterisation was avoided in order to prevent infection, and it is therefore impossible to give the precise urinary volume produced during each day of the oliguric stage The calculated mean daily volume during the first six days was 75 ml and the mean of the whole oliguric stage was 150 ml, suggesting a slow increase of urinary volume during this stage of the disease

The mean duration of the oliguric stage was 12 5 days (S D 5·0 days), which is similar to the mean duration reported by Bull et al (1950) and Swann and Merrill (1953) The rate of rise of blood-urea was greater during the first two days of the oliguric stage than in the succeeding days (fig 1), the mean blood-urea rising to 200 mg per 100 ml by the end of the second day This probably reflects a temporary increase of catabolism with a greater production of urea by breakdown of tissue proteins due to the initial insult. In addition, the rate of loss of urea in the small amounts of urine produced and in sweat, vomit, and fæces is roughly proportional to the concentration of urea in the blood After the second day, the rate of rise of blood-urea was reduced by treatment, and averaged 34 mg per 100 ml per day In some patients the rate of rise of blood-urea was not greater than 25 mg per 100 ml per day, which represents the theoretical minimum assuming a low endogenous protein breakdown of 40 g per day (Gamble 1951) In 3 patients the rate of rise of blood-urea was unusually great and hæmodialysis was required early in the oliguric stage 1 patient had an acute hæmolysis due to arsine poisoning, another had severe staphylococcal pneumonia, whilst the 3rd had leptospirosis with considerable liver damage. In all 3 cases there was probably an increased rate of protein breakdown from the associated condition

Of the 28 patients 13 were treated by hæmodialysis 11 had a single treatment, and 2 were dialysed on two occasions After the fifteen dialyses (twelve in the oliguric stage and three in the early diuretic stage) the subsequent daily rise of blood-urea continued unchanged (fig 2) Hæmodialysis causes the biochemical changes to revert to those found earlier in the oliguric stage, and has no other influence on the course of the disease. The rate of rise of blood-urea on the first day after hæmodialysis is usually greater than on succeeding days (fig 2) This probably reflects equilibration of the relative excess of urea in the intracellular compartment with that in the extracellular fluid and plasma. The artificial kidney clears urea first from the blood and extracellular fluid

Early Diuretic Stage

Division of the diuretic stage into an early and late stage is of great clinical value because the amount of urea excreted during the early diuretic stage is approximately equal to that formed from endogenous protein breakdown, and there is usually no fall of the blood-urea Indeed, during the early diuretic stage the clinical and biochemical

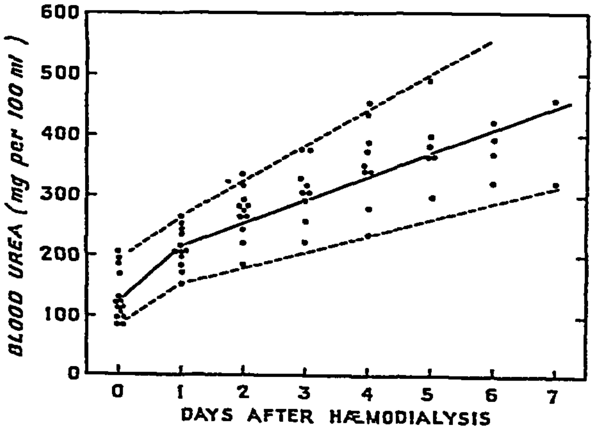

Fig 2—The rise of blood-urea during the oliguric stage of acute tubular necrosis after hæmodialysis

The rate of rise is greater on the first day after dialysis Subsequently the mean rise is identical with that shown in fig 1

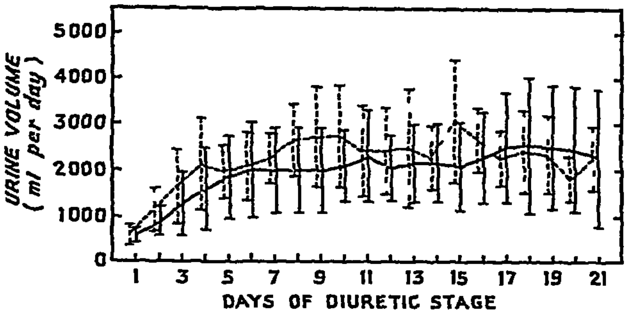

Fig 3—Urinary volume per day in the diuretic stage of acute tubular necrosis Continuous lines show the results from the present series, interrupted lines the results of a similar series treated by Bull et al. with a greater fluid intake during the oliguric stage, with mean and standard deviations in each case

The mean volume in the series of Bull et al is consistently greater until the 17th day of the diuretic stage

status of the patient does not improve and frequently continues to deteriorate In the late diuretic stage, however, when the blood-urea falls, there is steady and progressive improvement Hæmodialysis may have to be carried out in the early diuretic stage, but is rarely, if ever, indicated in the late diuretic stage As soon as the daily urinary volume consistently exceeds 400 ml there is usually a steady daily increase at a mean rate of 280 ml per day until a volume of about 2000 ml per day is reached after five or six days (fig 3) Thereafter the mean daily urinary volume is stabilised at 2000–2500 ml The mean duration of the early diuretic stage was 4 7 days (S D 3 1), and stabilisation of the urinary volume roughly coincided with the day on which the blood-urea started to fall

Late Diuretic Stage

Urine volumes in the late diuretic stage are now less than in cases treated ten to twelve years ago (Bull et al 1950) It was then customary to give patients more fluid during the oliguric stage—usually 1000 ml more than the total fluid loss on the previous day In fig 3 the mean urinary volumes in the present series are compared with those in a similar series of cases of acute tubular necrosis reported by Bull et al (1950) The mean urinary volumes are consistently higher in the latter series until the seventeenth day of the diuretic stage ($y^2=95$, P<0 001) If it is assumed that the patients of Bull et al received an excess fluid intake of 500 ml each day during the twelve days of the oliguric stage, average total excess given to each patient was 6 lit Comparison of the urinary volumes in fig 3 shows t the patients of Bull et al, on an average, each excre 6 5 litres more urine than the patients of the pres series during the first seventeen days of the diuretic sta This suggests that the greater diuresis in the patients the earlier series was largely due to the higher fluid inta during the oliguric stage It has been claimed (Bl 1957) that high urinary volumes in the diuretic stage acute tubular necrosis are chiefly due to osmotic diure the osmotic load per single functioning nephron be abnormally high. The observations recorded h suggest, however, that at least part of the diuresis patients treated in the past was due to water diure from prior over-hydration Whereas an individual w normal renal function would excrete an excess body-wat content of 6 litres within twenty-four hours, a patie in the diuretic stage of acute tubular necrosis has gr impairment of renal function (Swann and Merrill 195 and requires over two weeks to excrete excess water wh

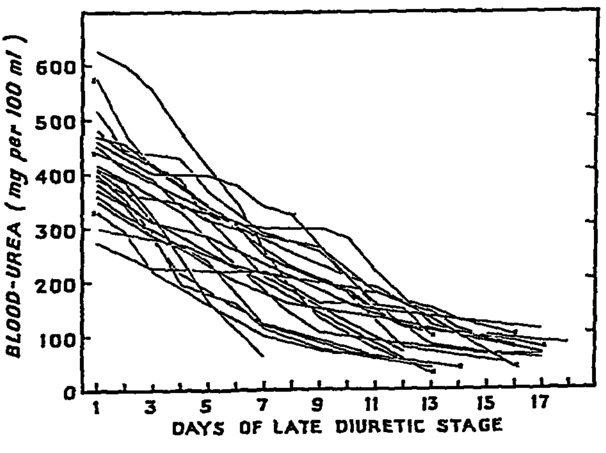

Fig 4—The actual fall of blood-urea in 20 cases of acute tubular necrosis during the late diuretic stage Crosses indicate cases treated by hæmodialysis

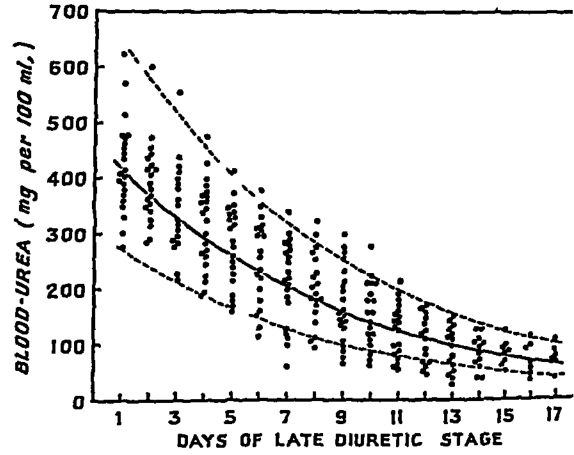

Fig 5—The fall of blood-urea during the late diuretic stage of acu tubular necrosis The logarithmic regression-line and limits twice the standard deviation are shown

could be eliminated by healthy kidneys within a singl day An excess body water content of 6 litres is equivalen to 13% of the normal total body-water and could caus considerable water intoxication.

During the late diuretic stage there is a progressiv exponential fall in the blood-urea (figs 4 and 5) On a average, the blood-urea becomes normal within seventee days (fig 5)

Convalescent Stage

By the end of the late diuretic stage the patient ha passed through a long and serious illness which has laste on an average five weeks (fig 6) During this perio there has been little or no intake of protein Althoug modern conservative therapy reduces endogenous protein breakdown, often to a value as low as 40 g per day, five weeks of protein starvation causes a loss of at least 1 5 kg of body-protein—about an eighth of the total body content The majority of this endogenous protein is derived from voluntary muscle The patient at the start of the convalescent stage is still an invalid, characteristically weak and often unable to stand or walk unaided Further recovery, however, is very rapid, the patient usually develops an insatiable appetite and quickly gains weight with increase of muscle mass and restoration of muscle

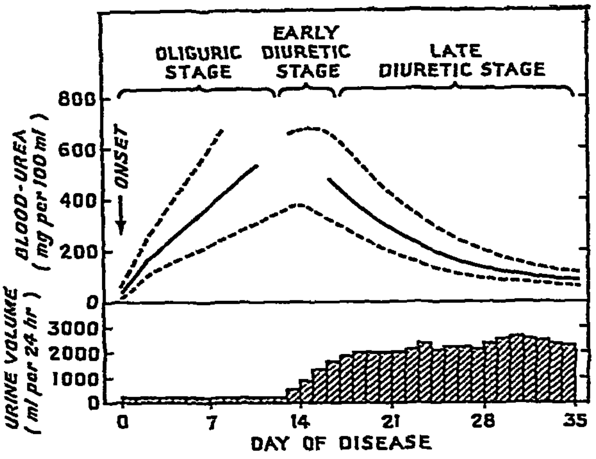

Fig 6—Graphical representation of an average case of acute tubular necrosis which summarises the previous charts.

The regression-lines of blood-urea and the upper limit at twice the standard deviation for the oliguric and late diuretic stages are not continuous in this series, because many of the patients were treated by hæmodialysis in the last few days of the oliguric stage

strength Usually it is at least two or three months from the start of the illness before the patient is well enough to resume full activities and duties

CLINICAL COURSE OF FATAL CASES

Of the 11 fatal cases (table II) originally diagnosed as uncomplicated tubular necrosis, all were examined at necropsy 3 cases, all due to concealed accidental hæmorrhage of pregnancy, were found to have had severe bilateral renal cortical necrosis causing irreversible renal damage We prefer to avoid percutaneous renal biopsy during the oliguric stage of acute renal failure, and therefore have no means of differential diagnosis between renal tubular necrosis and renal cortical necrosis except the response to therapy The apparent mortality in this series was therefore 28%, but the true mortality excluding the cases of renal cortical necrosis was 22%—a figure similar to those in other reported series

Of the 8 fatal cases of acute tubular necrosis, 4 died in the oliguric stage, 2 in the early diuretic stage, and 2 in the late diuretic stage They showed no obvious biochemical differences from the patients who survived, and the oliguric stage of the 4 patients who died in the diuretic stage was not unusually long Table II shows that sepsis, usually from organisms resistant to most available antibiotics, was the main cause of death

Of the 3 fatal cases of renal cortical necrosis 2 also died as a direct result of infection, although the severity of their renal lesion would have precluded final recovery 2 of these 3 patients died in the oliguric stage, on the ninth and eighteenth days The 3rd patient passed into an early diuretic stage on the twentieth day of her illness, and the urine output rose to a maximum of 970 ml per day before death on the twenty-ninth day This shows that a guarded prognosis should be given in all cases of acute oliguric renal failure due to concealed accidental hæmorrhage of pregnancy, unless the patient has passed into the late diuretic stage with a steadily falling blood-urea Even if percutaneous renal biopsy in such cases showed only acute tubular necrosis, this would not preclude renal cortical necrosis in other parts of the kidneys

Discussion and Summary

The average course of uncomplicated acute tubular necrosis is summarised in fig 6 Average durations of the first four stages of the disease are plotted on the abscissa, and the blood-urea and mean urinary volumes on the ordinate. The regression-lines for blood-urea and the upper limits at twice the standard deviation for the oliguric and diuretic stages are not continuous because almost half the patients were dialysed at the end of the oliguric stage Hæmodialysis artificially reduces the blood-urea at the start of the early diuretic stage It is almost certain that some of the patients would not have survived had hæmodialysis not been applied. Since the rate of climb of the blood-urea during the oliguric stage is identical before and after dialysis (figs 1 and 2), it is permissible to extrapolate the rise of blood-urea after dialysis to that before treatment in order to estimate the eventual level had dialysis not been carried out In the 2 patients who required dialysis on two separate occasions, the blood-urea would have been expected to rise to 1020 and 1110 mg per 100 ml Although in isolated cases recovery has followed the recording of similar levels of blood-urea, most such patients will die without hæmodialysis

This paper may prove useful to those responsible for the decision to transfer cases of acute tubular necrosis to a centre with facilities for hæmodialysis Although the duration of the oliguric stage in any single case remains unpredictable, the course of the oliguric stage may be accurately predicted after only a few days' careful observation The course of cases with severe tissue damage cannot be predicted Deterioration may be extremely rapid, and in these cases a high plasma-potassium or a low plasma-bicarbonate may provide urgent reasons for hæmodialysis before the blood-urea exceeds 400 mg per 100 ml.

Thanks are expressed to Prof G M Bull for permission to publish urinary volumes of patients under his care, and to Prof J McMichael and Prof E J King for advice

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CRYPTOGENIC LIVER ABSCESS

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Liver abscess is uncommon in Great Britain. Between 1950 and 1958 only 8 cases have occurred in 14,500 admissions to the Hospital for Tropical Diseases (U C.H), giving an incidence of 0 055% All these were shown to be amœbic in origin

With a chronic abscess in a patient at risk for amœbiasis it is sometimes difficult to be certain whether amœbæ were initially responsible for it and whether their presence has been obscured by superadded bacterial infection. There is a growing feeling, however, that pyogenic infection is becoming more important as a primary cause even in tropical practice (Worms 1956), and this is supported by McFadzean et al's (1953) figures from Hong Kong

During the decade 1949–58 6 cases of liver abscess have been seen in 183,000 admissions at University College Hospital in the general wards and in my private practice, giving an incidence of 0 003% None of these patients was at risk for amœbiasis, no amœbæ were found in any case, and it seems certain that they were pyogenic in origin This incidence agrees with de Bakey and Creech's (1956) estimate of 0 04–0 007% of all hospital admissions

Pyogenic organisms may gain access to the liver

1 From outside the body by trauma, which is self-evident

2 *Via* the hepatic artery, in which case systemic blood-culture should be positive

3 *Via* the bile-duct, when prominent early jaundice is to be expected

4 *Via* the portal vein In this group primary disease in the alimentary tract may be demonstrable (Dieulafoy 1898, Ochsner et al 1938, Shallow et al 1945, Champeau 1956), and a consideration of the venous drainage alerts the doctor to the possibility of hepatic spread

Diagnostic difficulty arises when no primary lesion is apparent and the liver abscess itself produces the presenting symptoms 4 of the 6 cases seen in the past decade fall into this group

Case-records

Case 1 —A 78-year-old lady developed malaise, nausea, and vomiting on April 27, 1957 She had had appendicectomy for recurrent lower abdominal pain many years before, and had also suffered from cataract and allergic rhinitis, and had bilateral operations for carpal-tunnel syndrome She was afebrile and there was no alteration in bowel habit, though other members of the household had recently had gastroenteritis

When seen on May 4 she was mentally confused and clinically anæmic Upper abdominal pain had appeared and there was slight tenderness across the epigastrium but no other abnormal physical signs During the next fortnight fever appeared and she developed a leucocytosis of 20,000 (90% neutrophils) Her hæmoglobin fell from 88% to 70% The erythrocyte-sedimentation rate (E S R) was 52 mm in first hour (Westergren) Blood-culture was sterile Liver dullness was increased, though the edge of the liver was never palpable, and movement of the right diaphragm became reduced X-rays showed a high right diaphragm and an enlarged liver shadow She was never jaundiced Her confusion increased to such a point that lumbar puncture was performed (demonstrating a normal cerebrospinal fluid) and a psychiatric opinion was taken before a diagnosis of liver abscess was made

After preliminary treatment with penicillin and streptomycin, the upper part of the right lobe of the liver was explored on May 23 after resection of the 12th and 11th ribs A soft area was found from which thin yellow offensive pus was aspirated An abscess 2 × 2 in was drained Moderate numbers of gram-positive cocci and bacilli were seen in a smear of the pus, and it was thought that the lack of significant growth on culture after seven days indicated that these organisms were probably delicate anaerobes

Her confusion disappeared and she made an uninterrupted recovery She has since remained well

Case 2 —A publican's 33-year-old wife had complained of right-sided abdominal pain for six weeks before she was seen on May 7, 1957 During this time she had been febrile on and off and feeling generally unwell Her waist measurement had increased by 2 in though her weight had decreased She remembered having had a short attack of lower abdominal discomfort and diarrhœa four months previously, but her bowels had always been erratic. She had previously suffered from asthma and neurodermatitis and was highly strung

She was ill and clinically anæmic, and there was muscular guarding and some tenderness in the upper abdominal quadrants, especially on the right, but there were no other abnormal signs Her urine contained no pus and was sterile Hæmoglobin 72% White cells 10,400 (69% neutrophils), E S R 54 mm in first hour

She declined admission to hospital till June 10, when her temperature had risen to 105° She was very ill, the area of liver dullness was enlarged, but no liver edge could be felt She became very slightly jaundiced (serum-bilirubin 1 8 mg per 100 ml) and the urine contained bilirubin A few râles appeared at the right lung base and she was treated with penicillin and streptomycin Flocculation tests were normal and blood-culture sterile

She improved temporarily and her jaundice disappeared, but persistent pain, localising tenderness, increasing leucocytosis, and falling hæmoglobin (55%) led to a diagnosis of liver abscess in the anterior part of the right lobe X-rays showed some elevation of the right diaphragm and enlargement of the liver shadow This abscess was drained per abdomen in July, 1957, but she had a stormy postoperative course and further drainage was necessary twice

Sinograms showed that the abscess extended high up into the anterior part of the right lobe (figs 1 and 2) The pus grew a microaerophilic streptococcus and *Streptococcus fæcalis* After the second recurrence of the abscess she was treated with prednisone in addition to appropriate antibiotics because the antibiotics might not be reaching the abscess cavity, her general condition had by this time improved a great deal and she was regaining her lost weight On the tenth day of this treatment she had a brisk hæmatemesis which demanded transfusion, and a barium meal showed a large gastric ulcer half-way down the lesser curvature, this did not communicate with the abscess and had given no previous symptoms Prednisone was stopped and she made a slow, steady recovery Intravenous cholangiography with iodipamide methylglucamine ('Biligrafin') showed a normal biliary tract She has since remained well

Case 3 —A 74-year-old lady had been well until an unexplained attack of diarrhœa, probably infective, at the age of 71 When first seen on Oct 7, 1958, she complained of anorexia, malaise, and fatigue for ten days, and pleuritic pain in the right lower chest for three days She was ill and anæmic but not jaundiced There were signs of aortic stenosis but no congestion of neck veins, though there was pitting œdema of both legs up to the knees Liver dullness was increased, but the liver edge was not definitely felt and was not tender There were signs of a small right pleural effusion and a friction rub high in the right axilla Her temperature was 100°, hæmoglobin 52%, and white cells 15,000 (88% neutrophils) E.S R 76 mm in first hour X-rays showed a high right diaphragm and a small right pleural effusion which contained many white cells, predominantly lymphocytes, and was sterile

She was transfused but remained very ill till Oct 24, when she coughed up 100 ml of foul-smelling pus which grew an

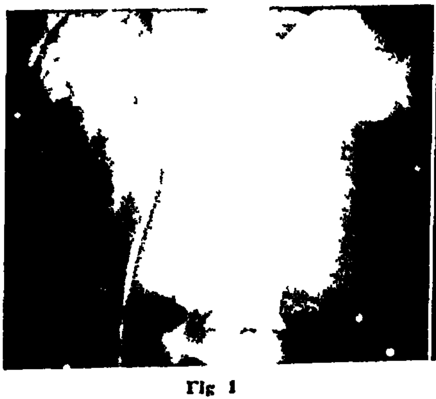

Fig 1

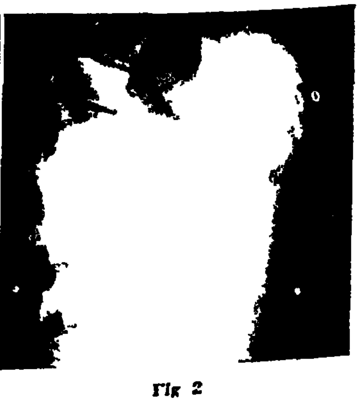

Fig 2

Fig 1 (case 2)—Sinogram Postero-anterior view showing abscess cavity

Fig 2 (case 2)—Sinogram Lateral view showing position of the abscess cavity in the anterior part of the right lobe of the liver

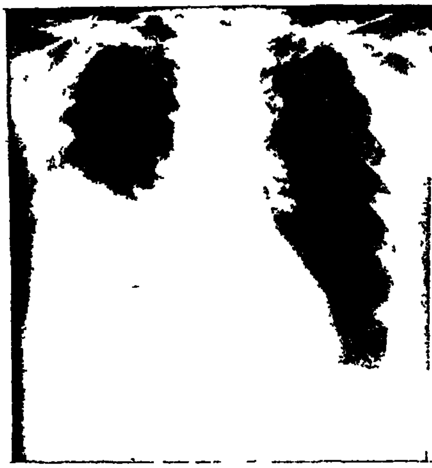

Fig 3

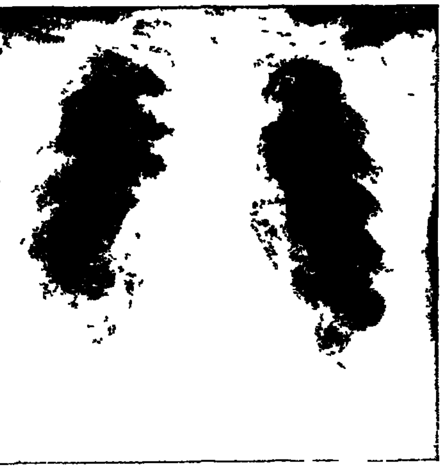

Fig 4

Fig 3 (case 3)—Postero-anterior view of chest on Oct. 31 after the abscess had burst into the lung

Fig 4 (case 3)—Postero-anterior view of chest showing some residual shadowing in the right lower lobe with return of the diaphragm towards the normal position

anaerobic streptococcus It grew no tubercle bacilli and contained no cancer cells or amœbæ. She was treated with penicillin and streptomycin and postural drainage and became afebrile on Oct. 31 (fig 3) Mental confusion, which had been a feature of her illness, gradually lessened and she made a slow, steady recovery, leaving hospital on Nov 23

When last seen on March 3, 1959, she had recovered her normal energy and was leading a very active life Her hæmoglobin was 84% A few râles could still be heard at the right base and the X-ray had not completely cleared (fig 4) She had no cough but she probably has some residual fibrosis in the right lower lobe She remains well

Case 4 —A 61-year-old man had had an appendicectomy at 19 and had then remained well (apart from an attack of urinary infection at 58) till he developed fever, malaise, and anorexia in July, 1955 There was a slight pleural reaction at the right base and a leucocytosis of 19,700 (84% neutrophils) He recovered after a month in hospital but had to be readmitted on Nov 11, 1955, because of malaise and upper abdominal pain. The liver was enlarged and tender, and over the next three weeks a mass continuous with the liver appeared in the right loin Laparotomy showed this to be a large abscess in the right lobe of the liver, offensive pus, which grew anaerobic cocci, was drained through the loin. He made an interrupted recovery on penicillin and streptomycin and returned to work two months later

Discussion

Pathogenesis

From the clinical standpoint all these abscesses were cryptogenic, though in retrospect there may have been slender clues to their site of origin in the diarrhœa previously sustained by case 2 and in the gastroenteritis of other members of the household of case 1

de Bakey and Creech (1956) thought that about half of all pyogenic abscesses are cryptogenic Rothenberg and Linder (1934) believed that they are caused by hæmatogenous spread from unrecognised distant systemic foci, while Beaver (1931) regarded them as the result of quiet infection in areas drained by the portal tract The presence of anaerobic cocci in my four cases supports Beaver's concept, and it seems possible that intercurrent gastrointestinal infection can allow increased entry of gut bacteria into the portal system through an inflamed intestinal mucosa—these organisms occasionally gaining a foothold in the liver despite its liberal network of vascular anastomoses and abundant supply of phagocytes

Diagnosis

Bourne (1954) has emphasised the importance of early diagnosis if high mortality is to be avoided

Liver abscess should be suspected wherever there is fever of obscure origin accompanied by steady upper-abdominal pain Examination will show enlargement of liver dullness, even though the liver edge may not be palpable With an abscess in the upper part of the right lobe, the lower margin of the liver may be displaced downwards without becoming harder, and in determining the palpability of the liver edge firmness is more important than enlargement There may be tenderness over the liver and pain may be produced by percussion over the right lower ribs or by firm pressure in the intercostal spaces in this region Jaundice is absent, or slight and transient, as would be expected from a focal lesion of the liver not obstructing the main bile-ducts By the same token there is no indication, clinical or biochemical, of hepatocellular failure Mounting leucocytosis and a high right diaphragm afford supporting evidence, and, if the disease is firmly established, anæmia may follow

Mental confusion may be prominent in older patients This is a symptom which may be encountered in anyone of an advanced age with an acute infection, especially if he is anæmic It deserves special mention since it was a leading symptom in case 1

If diagnosis is delayed, the abscess may rupture into neighbouring organs—most often into the lower lobe of the right lung or pleural cavity as in case 3

Treatment and Prognosis

Antibiotic treatment must be combined with adequate drainage Ideally the organism should be cultured and its sensitivity determined, in this context the importance of anaerobic culture has been stressed in general by E J Stokes (1958) and in particular by Worms (1956) In practice, these cryptogenic abscesses so often yield anaerobic or micro-aerophilic cocci that penicillin and streptomycin, to which they are commonly sensitive, should not be withheld from an ill patient

Surgical rather than spontaneous drainage is desirable Ochsner et al (1938) found that rupture into neighbouring organs worsened the prognosis, and the fatality-rate in their series, if such complications were excluded, was 36%, contrasting with the 50% rate estimated by Eliason (1926) for all cases in pre-antibiotic days

The direct benefit of antibiotics and the greater safety they confer on surgical procedures are responsible for the better prognosis in these abscesses nowadays Case 2 had much the stormiest passage and this can be related to the position of the abscess in the liver (fig 2), which demanded transperitoneal anterior drainage Ill recumbent patients cannot drain their abscesses anteriorly, and a posterior approach is preferable whenever possible

Summary

Four cases of cryptogenic non-amœbic liver abscesses with recovery are described.

No primary source of infection was evident clinically Anaerobic cocci were isolated from the pus in each case An origin in the gut and spread via the portal vein is probable

The organisms were all sensitive to penicillin and streptomycin Recovery is attributed to the use of these drugs combined with effective drainage

My thanks are due to Dr E E Pochin for access to the records of case 4

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A TRIAL OF BACTERIAL VACCINES FOR THE COMMON COLD IN THE ROYAL AIR FORCE

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MANY attempts have been made to prepare bacterial vaccines for the prevention or attenuation of the common cold Their use has been based on the assumption that the stage of secondary infection might thereby be eliminated or reduced in severity Most of these vaccines have been prepared from mixtures of selected organisms, chosen because of their supposed pathogenicity

Of the numerous trials of such vaccines, the few in which controls were adequate have given disappointing results

Diehl et al (1938) made a carefully controlled study of three vaccines, one administered subcutaneously and two orally, with randomly selected controls receiving a placebo The group which received the subcutaneous vaccine had 25% fewer colds per person than the control group, but the groups receiving oral vaccines showed no advantage over the controls Diehl et al concluded that the vaccines had little or no practical value McGee et al (1944), in a well-controlled trial of two vaccines administered parenterally and three oral vaccines, found no clear evidence of a reduction in either the frequency or the severity of the common cold

In 1958, however, Ritchie reported a controlled trial in which autogenous bacterial vaccines reduced the severity of colds and the time lost from work due to colds and upper-respiratory infections in a group of factory workers

Throat and nose swabs and specimens of saliva were collected from all volunteers When the subject was included in the randomly selected group to be given vaccine, the vaccine was prepared from the whole mixed culture of these specimens, when he was to be a control the specimens were discarded and he was given injections of carbol saline instead Injections were given weekly for up to five months during the winter, but for administrative reasons about half the volunteers stopped having injections after 8 weeks, although records of their colds continued to be made to the end of the trial The numbers of colds in the inoculated and control groups were similar, but in the vaccinated group only 13% of colds passed from the prodromal to the fully developed stage, compared with 62% in the control group There was evidence, however, that those who did not continue with the injections lost fairly rapidly the resistance which they had acquired

These findings, if substantiated, might be of considerable importance to certain groups such as flying personnel in the Royal Air Force in whom the duration and severity of colds is a matter of concern It was decided, therefore, to conduct a trial in the R A F based on Ritchie's method, but modified to meet the practical demands of the situation The vaccines were prepared in the same way as Ritchie had prepared his, but the dosage schedule was modified, as weekly injections would not be welcomed by healthy men and would be difficult to arrange on an operational flying station Furthermore there seemed to be no theoretical reason why weekly injections should produce a better immunological response than a more usual course In addition to those receiving individual autogenous vaccines and a control group given phenol saline, a third group was given a " pool " vaccine prepared by mixing the culture washings from all the members of the group

Clinical and Laboratory Methods

Selection of Subjects

The trial took place between October, 1958, and the end of March, 1959, at R A F College, Cranwell, and at R.A F Stations Oakington and Thorney Island. Volunteers were obtained from among flying cadets and instructors, since they would be keen to cooperate in a measure which might help to keep them flying, and because they are kept under close medical supervision, particularly with regard to respiratory infections The importance of reporting all colds, however minor, to the medical officer before flying is constantly stressed and therefore complete records could be hoped for About a dozen non-flying officers were also included, but they were treated for the purposes of the trial as if they had been fliers All volunteers were told that some of them would receive a vaccine which might reduce the loss of flying-time due to colds and that some would receive an inert control, but that they would not know till after the trial which they had received.

Method of Vaccine Preparation

A single swab was used to sample the tonsillar region and the front of the mouth of each man. The swabs were inoculated over the whole of a blood-agar plate After overnight aerobic incubation at 37°C the plates were inspected Eight of those allocated to the autogenous-vaccine group and nine of those in the pool group showed a heavy growth of hæmolytic streptococci, to lessen the risk of reactions, men yielding these cultures were transferred to the control group and replaced in the appropriate vaccine group by randomly selected men whose cultures did not show hæmolytic streptococci The growth on each plate from the men in the two vaccine groups was then washed off with normal saline containing 0 5% phenol and diluted separately with the phenol-saline to an opacity corresponding to a strength of about 500 million per ml A pool vaccine was constituted in the same way by mixing the washings from all the men in the appropriate group The vaccines were heated in a water-bath to 60 C for 1 hour and each was tested for sterility by inoculating 0 5 ml into a tube of thioglycollate broth. The vaccines and the phenol saline were put into individual exactly similar vaccine bottles for each volunteer.

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Inoculation Procedure

A total of 320 volunteers was allocated to the groups to receive autogenous vaccine, pool vaccine, or phenol saline, by reference to a table of random numbers Each group was treated in an exactly similar manner Neither the volunteer nor the medical officer giving the injections was aware of what was being given. Injections were given into the deep subcutaneous tissues of the upper arm, a separate, dry-sterilised syringe being used for each subject. The first dose, which was given in early October, 1958, was of 0 1 ml.; the second dose a week later was 0·3 ml., the third dose, two weeks after the second, was 0·5 ml., a fourth, reinforcing, dose, also 0·5 ml., was given in mid-January, 1959 On a personal record card, which was prepared for each man, were noted the dates of his injections and reactions to them. Two men who had originally been in the autogenous-vaccine group were given pool vaccine for the reinforcing dose because their bottles of vaccine had been damaged.

Reactions to Inoculation

Reactions were generally trivial. After each of the injections about a third of those receiving the autogenous or pool vaccines and a few of the controls had slight redness, swelling, and soreness at the injection site for 24–48 hours. In the autogenous vaccine group 2 men had more severe local reactions with an accompanying local lymphadenitis, 1 of them after both the second and the third injections and the other after the reinforcing dose only In the pool vaccine group 1 man had a severe local reaction accompanied by mild general malaise following the reinforcing dose. There were a few mild general reactions after each of the injections in the pool and autogenous groups but none in the control group 1 man in the autogenous-vaccine group experienced symptoms similar to allergic rhinitis starting 6–9 hours after each of the first three injections and clearing up in 48 hours, owing to release from the Service he did not have a reinforcing dose.

Recording Methods

Volunteers were urged at the beginning of the trial and reminded at intervals to report to their medical officer all respiratory infections however mild they might be. In this way, and because all flying personnel are well aware of the dangers of flying with a cold, it is believed that reasonably complete records were obtained. The assessment and the record of each illness were made by the station medical officers As stated above, neither they nor the volunteers knew who had received the vaccines and who the saline control. The date of each illness reported and the diagnosis were noted on the back of the personal record card. To support this entry an illness record card was completed for each illness On one side of this card were recorded certain features of the severity of the illness, including the number of days off full flying duties, a diagnosis, and an assessment of whether the illness was mild, average, or severe, taking into account both diagnosis and the patient's usual experience. The number of days off full flying duties included weekends, and where the man was on leave or off flying duties for any other reason the number of days that he would have been off duty was assessed. On the reverse side of the card were recorded the presence and severity of the following symptoms and signs within 48 hours of onset and after 48 hours nasal discharge, sinus pain, postnasal drip, cough, sputum, and negative Valsalva sign. When a volunteer was absent from the station or omitted to report an illness when it occurred, a record card was completed as far as possible in retrospect. Uniformity in the compilation of records between the units taking part was ensured as far as possible by monthly visits to each of the stations

Of the 320 original volunteers, 293 received all three initial injections and were followed for at least 1 month after the third dose. These were considered to be the minimum qualifications for inclusion in the final assessment of results A further 17 volunteers left their stations at various times during the subsequent course of the trial, and another 8 men did not receive the reinforcing dose for various administrative reasons Owing to these losses and also to some variation in the dates of injection the total period of follow-up tended to vary slightly with individuals, but it was found that the total numbers of weeks of exposure in each of the two vaccine groups and the control group were almost identical. Therefore the slight variations in the numbers and periods of follow-up were ignored.

TABLE I—INCIDENCE OF ALL RESPIRATORY ILLNESSES
(Attack-rates (%) in parentheses)

—	Autogenous vaccine	Pool vaccine	Control group
Total no. of volunteers	99	97	97
Total no. of illnesses	116 (*117%*)	119 (*123%*)	124 (*128%*)
Illnesses 3–6 weeks (incl.) after 3rd and reinforcing doses	34 (*34%*)	53 (*55%*)	52 (*54%*)
Illnesses during remainder of trial	82 (*83%*)	66 (*68%*)	72 (*74%*)
Illnesses 1–2 weeks after 3rd and reinforcing doses	43 (*43%*)	33 (*34%*)	28 (*29%*)
Illnesses during remainder of trial	73 (*74%*)	86 (*89%*)	96 (*99%*)

Results

The sickness records were analysed separately for the incidence and severity of all respiratory infections during the total period from the last of the three initial doses of vaccine to the end of the trial, and for two shorter periods within this time. (1) the period when the maximum effect of a normal immunological response would be expected, 3–6 weeks after inoculation, and (2) the period when the effects of any immediate but shortlived immunity would be expected, in the first 2 weeks after inoculation

TABLE II—NUMBER AND PROPORTION OF ILLNESSES CLASSIFIED AS MILD

Illnesses	Autogenous vaccine	Pool vaccine	Control group
Total	51 (*44%*)	51 (*43%*)	50 (*40%*)
3–6 weeks (incl.) after 3rd and reinforcing doses	10 (*29%*)	24 (*45%*)	17 (*33%*)
During remainder of trial	41 (*50%*)	27 (*41%*)	33 (*46%*)
1–2 weeks after 3rd and reinforcing doses	21 (*49%*)	9 (*27%*)	12 (*43%*)
During remainder of trial	30 (*41%*)	42 (*49%*)	38 (*40%*)

Table I shows the sickness incidence for all respiratory illnesses during the periods defined above. The total illness-rates in the three groups were about the same, but during the period from the 3rd to the 6th weeks after inoculation those in the autogenous-vaccine group had significantly fewer illnesses than the controls

$$\left(\frac{\text{Difference}}{\text{Standard error}} = \frac{20}{7} = 2{\cdot}9\right)$$

On the other hand the sickness-rates in the autogenous-vaccine group were higher than in the controls during the remainder of the trial

Table II shows the proportions of illnesses which were classified as mild. There was little difference in the severity of illnesses in the three groups shown by this method of assessment in each of the selected periods

TABLE III—NUMBER AND PROPORTION OF ILLNESSES INVOLVING THE LOSS OF MORE THAN 3 DAYS' FLYING-TIME

Illnesses	Autogenous vaccine	Pool vaccine	Control group
Total	54 (*47%*)	64 (*54%*)	68 (*55%*)
3–6 weeks (incl.) after 3rd and reinforcing doses	18 (*53%*)	24 (*45%*)	28 (*54%*)
During remainder of trial	36 (*44%*)	40 (*61%*)	40 (*56%*)
1–2 weeks after 3rd and reinforcing doses	14 (*33%*)	20 (*61%*)	15 (*54%*)
During remainder of trial	40 (*55%*)	44 (*51%*)	53 (*55%*)

TABLE IV—NUMBER AND PROPORTION OF ILLNESSES IN WHICH PURULENT SYMPTOMS OR SIGNS PERSISTED MORE THAN 48 HOURS FROM ONSET

Illnesses	Autogenous vaccine	Pool vaccine	Control group
Total	54 (*47%*)	66 (*55%*)	68 (*55%*)
3–6 weeks (incl) after 3rd and reinforcing doses	13 (*38%*)	27 (*51%*)	26 (*50%*)
During remainder of trial	41 (*50%*)	39 (*59%*)	42 (*58%*)
1–2 weeks after 3rd and reinforcing doses	19 (*44%*)	16 (*48%*)	19 (*68%*)
During remainder of trial	35 (*48%*)	50 (*58%*)	49 (*51%*)

It was particularly relevant to this study to know whether the volunteers who were vaccinated lost less flying-time than the controls Table III shows that they did not, except to a small degree during the first 2 weeks after inoculation with autogenous vaccine

If the vaccine were effective in shortening the stage of secondary infection of colds, fewer of the vaccinated persons would be expected to show purulent symptoms lasting more than 48 hours from onset than the controls In fact, as is shown in table IV, this was so for those receiving the autogenous vaccine, mainly in the period immediately following inoculation but also to some extent in the period 3–6 weeks after inoculation, although in neither instance was the reduction very great

Illnesses diagnosed as common cold formed 86% of the total and were almost equally distributed among the two vaccine groups and the controls All results were substantially the same when these illnesses were considered separately

Comment

It is clear from these results that autogenous bacterial vaccines as administered by us are unlikely to have any practical application in dealing with the problem of the common cold among flying personnel of the Royal Air Force There was, however, an interesting reduction in the incidence of illness in the autogenous-vaccine group in the period when it might be expected, between the 3rd and 6th weeks after inoculation Although there is little supporting evidence of reduced severity or duration of those colds which were reported during this period, there was some reduction in the number in which purulent symptoms persisted These observations are difficult to explain, since a vaccine designed to prevent secondary bacterial infection would be expected to reduce the severity of illnesses rather than their incidence Possibly, however, the reduction in severity of some colds was such that it led to under-reporting of these mild incidents Our results thus stand in contrast to those of Ritchie, but our volunteers received only four injections, whereas his were given them weekly for at least 8 weeks and many for the whole winter It is also possible that flying personnel of the R A F, who are carefully selected on medical grounds, suffer less from the bacterial complications of the common cold than factory volunteers, a proportion of whom were subject to heavy colds Autogenous bacterial vaccines, perhaps in greater dosage, may therefore merit further investigation among less healthy persons

Summary

A controlled trial of autogenous bacterial vaccines for the common cold among 293 flying personnel of the Royal Air Force is reported Three groups were formed and given autogenous vaccine, a pool vaccine, or phenol saline in a course of three initial doses in October, 1958, and a reinforcing dose in January, 1959 The volunteers were observed until the end of March, 1959, and records were made of all their respiratory infections during this time

The total incidence and severity of respiratory illnesses in the three groups were very similar, and such vaccines are, therefore, unlikely to have any practical application to the problem of the common cold among flying personnel of the Royal Air Force There was, however, a statistically significant reduction in the illness attack-rate in the autogenous-vaccine group during a limited period of 3 to 6 weeks after the third and reinforcing doses

Our thanks are due to the medical officers at R A F College, Cranwell, and at R A F Stations Oakington and Thorney Island for their valuable cooperation and assistance with every stage of this investigation, and to the Director-General of the Royal Air Force Medical Services for permission to publish the results

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DYSPEPSIA DUE TO INHALATION OF CARBON TETRACHLORIDE VAPOUR

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PATIENTS often blame their work for their indigestion, though this symptom is rarely directly attributable to occupation Any common symptom may, however, arise from work and the connection may be missed unless one asks in detail what are the actual processes involved Even then the patient may be unaware of the toxic nature of the materials that he uses, and the poison responsible may play a minor role in the main process on which he is engaged

A man of 34 years of age attended Poplar Hospital complaining of anorexia, nausea, and occasional vomiting with a feeling of abdominal discomfort not amounting to pain He had had these symptoms intermittently for two years, and on this occasion for about two months, during which time he felt unusually depressed and irritable No abnormal signs were found on clinical examination

One odd feature in the history—that the dyspepsia was better at weekends and built up during the week—led to more detailed inquiry about the patient's work It was then found that he was exposed to the vapour of carbon tetrachloride, and that other workers had developed similar symptoms in the past few months and some had consulted their doctors A visit to the factory was arranged

Description of the Factory

There were 18 people—14 men and 4 women—employed in a workshop with an area of about 3000 sq ft, divided into two parts by a wooden partition which did not reach the roof The windows were kept closed, and there was no mechanical ventilation The room was heated by indirect gas convector heaters, each of which was connected to a flue passing through the roof On entering the room one could detect no atmospheric contaminant, but one could smell carbon tetrachloride in the immediate environment where it was used.

Process

The factory processes raw quartz in the manufacture of crystals for electronic equipment The quartz is examined for flaws, before being orientated and cut with diamond-impregnated saws After X-raying and further cutting, the crystal blanks are stuck by means of a resinous wax on to lapping plates and ground on carborundum. The crystals are cleaned in carbon tetrachloride to remove the resinous wax, etched with hydrofluoric acid, then further cleaned by being passed through solutions of chromic acid, distilled water, methylated spirit, and acetone, and finally dried in an oven. The crystals are adjusted to their correct frequency by the addition of gold, effected by electroplating in a gold-cyanide solution. Finally, the crystals are mounted and cleaned by being passed through the series of solvents again, starting with carbon tetrachloride. To facilitate the cleaning process, an ultrasonic vibration of about 40,000 cycles per second is passed through the carbon tetrachloride solution. About two Winchester quarts (five litres) of carbon tetrachloride are used weekly, although much of this is thrown away

When a beaker of carbon tetrachloride was placed in the ultrasonic cleaning apparatus, drops of carbon tetrachloride could be seen spraying out from the beaker, and the characteristic odour of its vapour was obvious Carbon tetrachloride could also be smelt in the vicinity of another bench, where the plates were cleaned with cloth dipped in the solvent.

Clinical Survey

Medical and occupational histories were taken from 17 of the 18 employees, and 16 of the 17 workers interviewed were examined clinically

Of the 17 workers seen, 15 complained of symptoms, which are shown in table I The pattern was similar in all Nausea was usually first noticed on a Tuesday or a Wednesday afternoon and increased in severity as the week progressed Anorexia was most severe for the evening meal These symptoms were accompanied in most cases by upper abdominal discomfort, which did not amount to pain, but was described as an unpleasant distended feeling The incidence of vomiting was more varied. In the more severe cases vomiting occurred up to four times in the day, usually on a Thursday or a Friday, and took place both at work and at home in the evenings

Of the remaining symptoms, depression was the most pronounced, and this was noticed by workers who had never had such feelings before. Complaints were made of irritability and of unusual shortness of temper with children at home. There were no complaints of lassitude or somnolence. In all but 2 of the workers the symptoms had first manifested themselves during the preceding four months, since the autumn of 1958, and were most severe in the weeks prior to our visit. This coincided with the closure of windows in the colder weather

The clinical examinations were performed five days after precautions had been taken to reduce further exposure. No abnormal physical signs were discovered The fundi and visual fields were normal 3 men had mild upper abdominal tenderness, but without guarding No abnormalities were found in the urine. Case 7 (table I) when originally examined in hospital had a raised serum-glutamic-oxalate-transaminase (76 units per ml), but this test was normal in this man and in 7 others at the time of the clinical examinations

TABLE II—ATMOSPHERIC CONCENTRATION OF CARBON TETRACHLORIDE IN DIFFERENT SITES IN THE WORKSHOP AFTER RUNNING THE ULTRASONIC EQUIPMENT FOR THREE HOURS (*a*) BEFORE COVERING BEAKERS CONTAINING CARBON TETRACHLORIDE, (*b*) AFTER COVERING THE BEAKERS

Site	Concentration of carbon tetrachloride			
	Before covering beakers		After covering beakers	
	Parts per million	mg per c.m.	Parts per million	mg per c.m.
Adjacent to ultrasonic apparatus				
Bench 1	97	620	8	50
Bench 2	70	450	9	60
Bench 3	67	430	0	0
On other side of partition				
Bench 4	45	290	<8	<50
Bench 5	47	300	<8	<50
Bench 6	45	290	<8	<50

Environmental Survey

The concentration of carbon tetrachloride in the atmosphere at different sites in the workshop was estimated after the ultrasonic equipment had been running continuously for three hours, and repeated after the control measures suggested were put into practice. The atmospheric samples were taken into two impingers in series with a handpump, carbon tetrachloride in the samples being estimated by the technique described by Strafford et al (1956) The results obtained at various sites in the workshop are given in table II A maximum allowable concentration in the atmosphere of carbon tetrachloride of 25 parts per million (160 mg per c.m) was recommended by the American Conference of Governmental Hygienists (1959) The concentrations obtained under the original conditions were considerably in excess of this recommended figure, as can be seen in table II, which also shows the effectiveness of the simple control measures instituted. The beakers containing carbon tetrachloride were covered, and the cleaning of plates with cloth dipped in carbon tetrachloride was stopped All the workers were symptom-free within one week, and there were no recurrences up to six months later

Discussion

That exposure to high concentrations of carbon tetrachloride produces narcosis, liver damage, and kidney damage is well known It is less well known, however, that exposure to lower concentrations may be responsible for less serious effects In a detailed investigation of workers subject to prolonged exposure to carbon tetrachloride, Stewart and Witts (1944) found a high incidence of gastrointestinal upset and mental hebetude. The symptoms were similar to those in our patients with the difference that diarrhœa was prominent in their group Their radiological investigations showed hypermotility with accompanying irritability and irregular contraction throughout the alimentary tract, and they suggested that these effects were produced by autonomic

TABLE I—SYMPTOMS PRESENT IN 17 WORKERS EXPOSED TO CARBON TETRACHLORIDE

—	Case no																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age (yr)	43	32	27	33	44	26	34	29	54	31	24	16	17	53	23	42	27
Symptoms																	
Nausea	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–
Anorexia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–
Vomiting	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Flatulence	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–
Epigastric discomfort or distension	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–
Depressive symptoms, headache, giddiness	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Duration of symptoms (mos)	4	4	2–3	2	2	24	24	2–3	0	½	2½	2	¼	2–3	1½	2½	0

stimulation They found no evidence of liver damage on liver-function tests, and they disputed the view of Elkins (1942) that such symptoms reflected an early stage of liver damage

Stewart and Witts were unable to measure atmospheric concentrations of carbon tetrachloride Smyth and Smyth (1936), on the basis of animal experiments and clinical studies, concluded that 100 parts per million of carbon tetrachloride in the atmosphere would be a reasonable maximum allowable concentration This figure has steadily fallen over the years to the present American level of 25 parts per million The findings presented here show that a concentration of carbon tetrachloride in the working environment of the order of 45–100 parts per million can be associated with the appearance of symptoms of poisoning

Summary

A group of factory workers developed nausea, and other symptoms increasing in severity in the latter half of each working week These symptoms were attributed to exposure to the vapour of carbon tetrachloride in a concentration of approximately 45–100 parts per million

We wish to thank Dr Donald Hunter and Dr A I G McLaughlin for their advice, and Mr E King, Mr P N Casbolt, and Mr D E Fine, of the Department for Research in Industrial Medicine, Medical Research Council, for carrying out the atmospheric sampling and analyses

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POLYNEURITIS AND CENTRAL HYPERTENSION DUE TO NON-PAROTITIC MUMPS

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THE nervous system is not infrequently involved in infections with the mumps virus A short, benign, lymphocytic meningitis is the commonest neurological complication of the disease and has been reported in as many as a third of infected patients (Holden et al 1946, Brown et al 1948) It may cause no symptoms and be detected only by routine examination of the cerebrospinal fluid

Involvement of the nervous system usually follows the development of clinically obvious parotitis within a period of a week Occasionally the parotitis may be delayed

Eberlein and Lynxwiler (1947) showed, in a review of 280 cases of mumps " meningoencephalitis " reported since 1918, that in about 10% of cases the neurological illness antedated the parotitis by several days In a further 13% of cases clinically evident parotitis did not occur at any stage of the illness In most instances the diagnosis was based on the occurrence of the characteristic neurological illness during epidemics of mumps, or in close contacts of known cases of parotitis In the more recent cases the diagnosis was based on the development, in patients with meningoencephalitis, of diagnostic changes in mumps antibody titre (Kane and Enders 1945) The occurrence of meningoencephalitis due to serologically proven mumps, without parotitis, is now well documented (Enders 1946, Kilham et al 1949, Kilham 1949, Adair et al 1953, Horstmann 1956, Overman 1959)

Involvement of the nervous system may on occasion show itself in the course of mumps by conditions other than meningitis Facial palsy, labyrinthitis, nerve deafness, and other localised forms of neuritis are well-known complications Encephalitis and myelitis, clinically and pathologically very similar to the parainfectious encephalomyelitis due to measles, rubella, and varicella (Miller et al 1956) may occur

Polyradiculitis and polyneuritis are extremely rare complications of mumps Miller et al (1956) could find only 9 cases reported between 1934 and 1956 Parotitis was present in every case, although in 3 instances it developed only after the onset of neurological symptoms

No cases appear to have been described hitherto of nonparotitic mumps presenting as polyneuritis We here report such a case, which had two further most unusual features—namely, severe and fairly long-continued hypertension of " central " origin and the onset of meningoencephalitic symptoms well after the development of frank polyneuritis Although " central " hypertension is a well-known feature of certain cases of bulbar poliomyelitis and has been reported in " acute infective polyneuritis " (Woltman and Kernohan 1955) it does not appear to have been previously described in " allergic " parainfectious polyneuritis or polyradiculitis

Case-report

Mrs A, aged 17, was admitted to Queen Charlotte's Hospital in the 32nd week of her first pregnancy and treated with streptomycin on account of a urinary infection Throughout this pregnancy her blood-pressure never rose above 130/80 mm. Hg On Dec 30, 1958, she gave birth, at term and by normal delivery, to a $6^{1}/_{2}$ lb boy On the second day of the puerperium mild pyrexia developed, and this persisted for two weeks On the eighth day she complained of " pins and needles " in her hands and feet and of an unsteady gait. She was found to have absent reflexes in the lower limbs and slight sensory impairment in both feet.

Apart from rheumatic fever in childhood she had always been healthy There was no personal or family history of epilepsy There had been no recent contact with any case of mumps

Investigations

The patient had mild normocytic anæmia (Hb 75%) and total white blood-cells 12,500 per c cm The Paul-Bunnell test was negative and blood-cultures were sterile The urine contained a trace of albumin and yielded a scanty growth of coagulase-negative *Staphylococcus albus* The blood-urea was 23 mg per 100 ml The cerebrospinal fluid (C.S F) was under normal pressure but contained 140 mg of protein per 100 *ml* , the cell count and sugar content were normal and the fluid was sterile on culture

On the basis of the clinical findings and of the albuminocytological dissociation in the C.S F , Guillain-Barré syndrome was diagnosed

Course

On the thirteenth day of the puerperium the patient had nine very severe generalised convulsions within a period of fourteen hours, and she remained unconscious for forty-eight hours For the first time her blood-pressure was found to be raised (180/130 mm Hg) White blood-cells had now increased to 18,000 per c mm The serum-electrolytes were normal and the urine contained 13 mg of protein per 100 ml and grew a β-hæmolytic streptococcus on culture A further lumbar puncture yielded C.S F containing 150 mg of protein per 100 ml , but only 1 lymphocyte per c.mm

The fits were treated with paraldehyde and chlorpromazine, and the patient was subsequently given sodium phenytoin (50 mg b d.) Lactation was suppressed by three injections of 15 mg of stilbœstrol, given on successive days, and the urinary infection was treated with a five-day course of chloramphenicol. Her blood-pressure remained persistently raised at 180/130 mm. Hg, and treatment with reserpine (0 25 mg b d.) was started.

During the following week her level of consciousness improved, but severe paralysis of the limbs developed. In view of this, the associated convulsions, and the persistently raised blood-pressure, she was transferred to Hammersmith Hospital on Jan. 19, 1959

Condition on Transfer

On admission the patient complained of severe occipital headache, double vision on looking to the left, circumoral parasthesiæ, and slight difficulty with speech and swallowing She was unable to move her limbs and could not turn about in bed. There were no paræsthesiæ in the limbs Sphincter control was not impaired. Temperature 98°F, no rash, lymphadenopathy, enlargement or tenderness of the salivary glands, or sternal tenderness, body-weight 84 lb Pulse-rate 120 per minute, blood-pressure 200/120 mm. Hg

The patient was apathetic and had mild meningism. The fundi were normal. She had bilateral external rectus pareses, coarse nystagmus on looking to the right and fine nystagmus on looking to the left, and some rotatory nystagmus on upward gaze, bilateral facial paresis, and mild bilateral palatal and pharyngeal palsies There was severe generalised symmetrical wasting of the upper and lower limbs with much associated weakness, especially distally, and moderate weakness of the trunk muscles

The muscles were tender and there were early contractures at the right elbow and ankle All the tendon reflexes were absent. The plantar responses were feebly flexor There was impairment of light touch and pain sense, and loss of vibration and postural sense in the hands, forearms, feet, and legs of "glove-and-stocking" distribution.

Further Investigations

The blood picture was normal. The erythrocyte-sedimentation rate was 25 mm. in the first hour (Westergren) The Paul-Bunnell test was again negative Serum-electrolytes, blood-urea, and liver function tests were normal The urine contained no albumin, porphyrins, or other abnormal constituents and was sterile on culture. The Mantoux test was negative at 1 10,000 The C.S F contained 490 mg of protein per 100 ml. but was otherwise normal. An intravenous pyelogram was normal

An electroencephalogram (E.E G) on admission showed a severe generalised abnormality with no normal rhythms present. It was dominated by very large bilaterally synchronous slow waves, most prominent precentrally and occasionally of higher amplitude on the right side.

As no obvious factors had been discovered to account for the polyneuritis and subsequent meningoencephalitis, serum was sent to the Central Public Health Laboratory, Colindale. At no stage were abnormal titres of antibodies against any of the known "respiratory" viruses found, but the following results were unexpectedly obtained

Date (1959)	*Day of disease*	*Mumps "virus particle" antigen*	*Mumps "soluble" antigen*
Jan. 13	6	1/32	1/16
" 23	16	1/64	1/32
Feb 19	43	1/8	1/8
March 13	65	1/8	1/8

These findings were interpreted by Dr C E D Taylor, of the routine diagnostic laboratory, Colindale, as strongly suggestive of recent infection with mumps virus The serum-amylase was normal.

Progress

The patient was given phenobarbitone (50 mg t.d.s) and sodium phenytoin (100 mg t.d.s), this was gradually reduced *pari passu* with the improvement in the E.E.G findings and was finally stopped when these findings had returned to normal. She received regular physiotherapy

Two days after admission to Hammersmith Hospital she had two further generalised convulsions, each lasting about two minutes, in which the only lateralising features were deviation of the head and eyes to the right. During the second attack her blood-pressure rose to 220/140 mm. Hg

The patient made steady and fairly rapid progress Four weeks after the start of her illness the bulbar signs had disappeared, and by the fifth week the external ocular movements were normal and she had no nystagmus or circumoral parasthesiæ, she could sit up and turn about in bed unaided. By the ninth week she could walk with assistance, and by the eleventh the sensory signs had cleared. The hypertension gradually subsided during convalescence, the blood-pressure eventually settling at 120/80 mm. Hg The E E G also reverted to normal. Three months after the onset of her illness the patient could walk unaided and normal menstruation had returned.

The only residual disability is moderate weakness of both anterior tibial muscles, causing partial bilateral foot-drop Improvement is continuing

Comment

Clinically this case resembled previously reported cases of mumps polyneuritis (Miller et al 1956) in the severity of the tetraplegia, its association with lower-cranial-nerve palsies, and the considerable albuminocytological dissociation of the C S.F The present case differed from the hitherto reported cases in the severity of sensory loss (rather an inconstant feature in previous cases and, when present, rarely extreme) and in the development of meningoencephalitis (nuchal rigidity, fits, and stupor), *subsequent to* the development of polyneuritis Of the various parainfectious neurological syndromes, polyneuritis has the longest latent period It is hardly ever followed by meningoencephalitis

The hypertension was assumed to be of "central" origin in view of its acute onset and eventual complete subsidence, the absence of any alternative cause, and the known association of hypertension with certain inflammatory disorders involving the brain-stem

The diagnosis of mumps in non-parotitic cases must of necessity rest on laboratory evidence Isolation of the virus from the C S F has proved feasible in a large proportion of cases of lymphocytic meningitis due to mumps (Kilham 1949, Kilham et al. 1949), but in patients presenting with other neurological disorders serological evidence has to be relied on In our patient the serum showed increases of complement-fixing-antibody titre equal to or exceeding the fourfold increase suggested by Kilham (1949), and subsequently accepted by others (Feller and Jordan 1950, Adair et al 1953, Horstmann 1956, Wolman 1957), as diagnostic.

We wish to thank Mr T L. T Lewis, who referred the patient to us, and Dr C. E. D Taylor, for his help with the serological investigations

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TREATMENT OF UNUSUAL CASE OF ANURIA

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THIS case of acute renal failure, treated by the conservative method of Borst (1948) and Bull et al (1949), presented unexpected and interesting features

Case-record

An unmarried woman, aged 48, had a rigor, followed by dysuria, frequency, and nocturia, ten days before admission on Oct 29, 1958 Nausea and retching began four days later She had occasionally had frequency and dysuria, for one to two days, throughout several years Since 1952 she had been incapacitated by rheumatoid arthritis, and, because of this, had taken 200 mg phenylbutazone daily for five weeks prior to admission She was in hospital in 1952, because of the arthritis, and in 1955, suffering from " pneumonia "

She had typical rheumatoid deformities Her temperature was 100 6°F There was no other abnormality on clinical examination, and her tongue was moist The urine contained many pus cells and fine granular casts, and culture showed *Escherichia coli* Albuminuria ($^3/_4$ part Esbach) and ketonuria were found, and the reaction to Benedict's solution was green The hæmoglobin level was 12 g per 100 ml , white blood-cells 10,600 per c mm , erythrocyte-sedimentation rate 96 mm in the first hour (Westergren), blood-urea 41 mg per 100 ml , serum-proteins normal The lupus-erythematosus-cell test, Wasserman reaction, and gonococcal fixation test were negative, and the Rose-Waaler test was strongly positive The fasting blood-sugar was 93 mg per 100 ml X-ray of chest and electrocardiogram were normal

Treatment and Course

Acute pyelonephritis was diagnosed, and treatment started with alkalis, fluids, light diet, and 'Sulphatriad' 1 g t i d Intake and output were satisfactory, though the patient vomited small quantities of fluid On the fourth day she complained of central abdominal colic, but no abnormality was detected Urinary output on the sixth day was only 235 ml Sulphatriad was discontinued, and four pints of 5% glucose given intravenously without effect The patient was anuric for eleven days She was placed on the regime outlined by Bull (1958) An intragastric drip was maintained for twenty-two days, during which 250–300 g glucose was given daily Vomiting was persistent, but the fluid lost was easily replaced Water and electrolytes lost through diarrhœa were replaced by equivalent fluids Antibiotics and vitamins were given orally The grave illness ran a typical course, with the highest blood-urea level—310 mg per 100 ml —on the eighteenth day The serum-potassium level was high at first, but with the high carbohydrate intake, and two injections of isobutyrate crystals of testosterone ('Perandren' 50 mg), it remained just within normal limits until diuresis began, when it fell to dangerously low levels which proved difficult to correct with intensive oral potassium

On the fourth day of anuria cystoscopy was performed The bladder was healthy, and the ureteric orifices were normal The ureteric catheter was held up at 1 cm on the left side Pyelogram of the right kidney was normal The few drops of urine in the bladder contained many pus cells, a very occasional red blood-cell, and, on culture scanty proteus and enterococci No crystals were seen Serum-sulphonamide was 4 2 mg per 100 ml

Two days later the patient was very ill, and rapidly became dehydrated and confused Her condition resembled that of a diabetic almost in coma. Blood-sugar at 3 P M was 760 mg per 100 ml Despite 24 units of soluble insulin, and oral saline (one-third physiological), it was 900 mg by 10 30 P M 60 units of soluble insulin brought the level down gradually to 100 mg at 9 A M Throughout the night the patient was paranoid, with Kussmaul respirations and rhonchi at the lung bases The danger of hyperglycæmia was now appreciated, and blood-sugar levels were controlled by insulin (see figure) With this, and control of infection, the patient slowly recovered. She developed a generalised drug rash after intramuscular tetracycline, and again after intramuscular penicillin

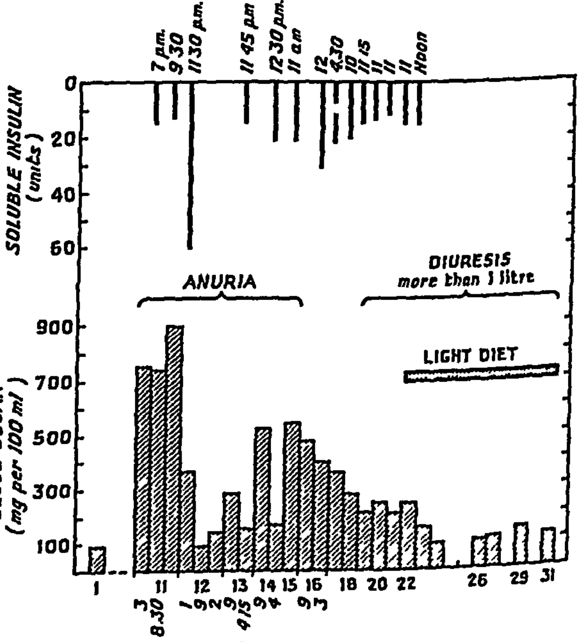
The first urine passed after eleven days, and blood taken at the same time gave blank values for phenylbutazone This was eighteen days after the last dose

On the thirtieth day of illness liver-function tests were found to be abnormal thymol flocculation+++, cephalin-cholesterol++++, prothrombin-time 27 sec., serum-albumin 3 2 g, globulin 3 2 g, per 100 ml These slowly became normal. Two oral, and one intravenous, glucose-tolerance tests gave diabetic curves, and also suggested abnormal leakage of glucose in the urine Urea-clearance was 29%, and maximum concentration of urine 1006 Seven months later an oral glucose-tolerance test was normal, concentration reached 1012, and urea-clearance was 45%

The case-notes for 1955 showed the the patient's previous illness had been acute pyelonephritis, with *Esch coli* infection, following phenylbutazone for several weeks Treatment was with sulphatriad and alkalis, but, because of vomiting, finally with tetracycline The urinary output was low on two occasions (7 oz , 14 oz) at times when intake was low

Discussion

This patient's history emphasises two points in the conservative treatment of acute renal failure (1) blood-sugar estimations are essential, and (2) insulin control of hyperglycæmia will probably be necessary Insulin is generally administered, primarily in order to promote the formation of glycogen and a potassium-glycogen cellular complex, to prevent a dangerously high serum-potassium level (Fenn 1940, Bywaters and Joekes 1948, Bull et al 1953) De Wardener (1958) refers to this, but not to the necessity for insulin control to prevent hyperglycæmia In the present case it was not appreciated that with a satisfactory potassium level hyperglycæmia would be so severe and would cause such physical and mental deterioration Tests suggested that carbohydrate control was probably disturbed, but at first it was known only that the patient



Blood-sugar levels and insulin dosage

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had a normal fasting blood-sugar. Evans et al. (1953) have pointed out the importance of routine blood-sugar estimations, since high levels develop in many cases. Rennie (1958) recommends that the blood-sugar be estimated every third day, and that 10 units of soluble insulin be given three times each day if the level much exceeds 250 mg. per 100 ml.

The cause of acute renal failure in this patient has not been accurately determined. She had an acute urinary infection and probably chronic renal infection, on admission. On ureteric catheterisation, however, there was no abnormality and no crystals were found. This suggested that the sulphonamide was not responsible, and the blood-sulphonamide level was low. Tests suggested hepatocellular damage, and an upset of carbohydrate metabolism, which, in association with abdominal pain, might have been due to pancreatitis or hepatitis. The patient had received 200 mg. phenylbutazone daily for five weeks, and had had a remarkably similar illness in 1955 following the same drug. Twice while in hospital she exhibited hypersensitivity to drugs. Her latest illness was probably due to idiosyncrasy to this drug associated with already poor renal function. During convalescence she appeared to have diminution in function of the proximal convoluted tubule, shown by daily glycosuria. This is a rare sequel to acute renal failure (Bull et al. 1950), but could be a nephrotoxic effect.

Toxicity of phenylbutazone can develop after small doses (Steel and Moffatt 1954, Wood 1954, Fraser 1955). In the case reported by Johnson and Larkin (1954) the patient had contracted kidneys and poor renal function, which they suggested should preclude the use of the drug. Toxic effects may occur after the drug has been stopped. Blood-levels fall over seven to fourteen days, and blank values are found after fourteen days (Bruck et al. 1954, Huffman et al. 1954, Wood 1954). Phenylbutazone has been reported as causing widespread visceral damage, including hepatitis, pancreatitis, and renal tubular damage and has caused acute renal failure (Bourne 1953, Freeland et al. 1953, Stifel and Bunheimer 1953, Bruck et al. 1954, Engleman et al. 1954, O'Brien and Storey 1954, Fraser 1955, MacCarthy and Jackson 1955). The most interesting parallel is with the case reported by Nassim and Pilkington in 1954, where the urine contained albumin, bile, urobilinogen, and granular casts a few days after phenylbutazone was discontinued.

Ten days later there was pronounced glycosuria and a diabetic glucose-tolerance curve, and the patient required insulin for ten days. Serum-amylase was normal, but liver-function tests were abnormal, and liver biopsy showed changes thought to be due to toxic damage. It was several months before liver-function tests and glucose-tolerance became completely normal. No previous case had shown transient hyperglycæmia responding to insulin. The involvement of so many viscera was thought to suggest a hypersensitivity reaction.

Summary

A case of acute renal failure, treated by conservative methods, is described.

Blood-sugar estimation is important in such cases, and hyperglycæmia must be controlled by insulin.

In the present case the cause was apparently hypersensitivity to phenylbutazone.

I thank all those in the unit and the Western Infirmary who worked so hard for this patient, and in particular Dr. James Reid for his advice and encouragement.

References at foot of next column

FIBROCYSTIC DISEASE OF THE PANCREAS IN A MAN AGED 46

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IN recent years patients with fibrocystic disease of the pancreas have been observed to reach greater age in a better clinical state than previously. Most of this improvement has been attributed to the use of antibiotics and other measures in controlling the pulmonary infection which so frequently causes death. But an increasing number of cases has been diagnosed in later childhood, and there have been predictions that cases would be discovered in adult life, especially where the full established clinical picture had not been present from birth (Andersen 1958). Andersen (1958) mentions a patient aged 35 years who was found at necropsy to have certain features suggestive of this condition, but she said that the diagnosis was far from established in that instance.

In the case described here a man aged 46 years presented with a combination of chronic pulmonary suppuration and pancreatic insufficiency, and he is thought to have fibrocystic disease of the pancreas.

Case-record

A shopkeeper, aged 44, was referred to one of us (B. L. M.) in April, 1958, with a history of cough and sputum for as long as he could remember, and certainly since the age of 2½ years. His sputum, which had always been yellow, had in recent years increased in amount to 2 oz. daily. He recollected wheezing in childhood, but this was abolished by coughing up his sputum. Each morning he spent a few minutes "clearing" his chest. Effort tolerance had been somewhat impaired for years, although he could still climb three flights of stairs quite briskly. There were days when he was more wheezy than usual, but the dyspnœa was constant. Purulent nasal discharge had been present since childhood. His nose was usually blocked and his sense of smell was poor. Colds were common. He had had pneumonia at the ages of 2½, 7, 10, 29, and 34 years, and had been severely ill on the last two occasions.

His mother did not consider him to be strong as a child, and he had always looked after himself carefully. His sisters were of normal height, but he was usually the shortest in his class. His appetite was always large, but for some years it had been voracious. He passed two motions daily during childhood, and

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Preliminary Communication

RELATION OF FREE CORTICOSTEROIDS IN URINE TO STEROID DOSAGE

In clinical practice the urinary excretion of 17-hydroxycorticosteroids—i e, 17(OH)CS—is a measure of whether a patient has excess hydrocortisone (cortisol) or is in need of it Experience has shown that excess is accompanied by above-average excretion, and deficiency by below-average excretion Recent studies of the protein binding of hydrocortisone show that the small diffusible fraction determines the clinical effectiveness of hydrocortisone, and that the diffusible fraction does not vary directly with the protein-bound fraction as the blood-level rises [1] This being so, assays of plasma hydrocortisone are not an accurate guide to the effective concentration of hydrocortisone, and it is not likely that the urinary excretion of 17(OH)CS is an accurate guide either

The excretion of free unmetabolised hydrocortisone in the urine may provide a measure of the effective (diffusible) fraction in the blood [2] Because of the recent protein-binding studies this suggestion can be tested, since one can predict from them how much hydrocortisone should appear in the urine if the excretion varies with the level of diffusible hydrocortisone

METHOD

To induce a steadily rising blood-level a normal subject took hydrocortisone daily in divided doses, increasing the dose by 20 mg every two days Twenty-four-hour specimens were collected under toluene, and the excretion of hydrocortisone, cortisone, and total 17(OH)CS was measured

Hydrocortisone and cortisone were measured by the methods of Bush,[3] with minor modifications suggested to us by Dr Bush Total 17(OH)CS was measured by the method of Appleby et al [4]

RESULTS

Fig 1 shows the mean excretion of hydrocortisone, in microgrammes, for each two-day period, and of total 17(OH)CS in milligrammes Except for the last three days' hydrocortisone excretion, the pairs of assays were too close to be depicted separately The rate of increase of hydrocortisone excretion is what could be predicted from the protein-binding studies

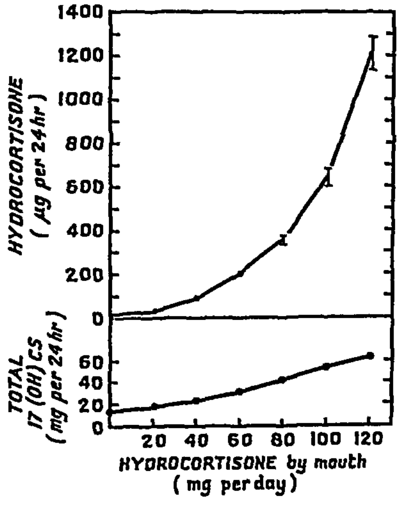

Fig 1—Increase in the absolute and relative excretion of hydrocortisone and total 17(OH)CS at successively higher doses of hydrocortisone

Fig 2, the curve of the excretion of hydrocortisone plus cortisone, is included because the biological significance of free cortisone in the blood is unknown

DISCUSSION

To know just how accurately the urinary free hydrocortisone reflects the diffusible level in the blood we must await more complex studies in which this blood-level is measured over the same period as the urinary levels Nevertheless our findings, which reasonably fulfil prediction, do show great disparity between the estimates from the excretion of free hydrocortisone and those from the excretion of 17(OH)CS metabolites They are consistent with the very considerable evidence that steroids act as catalysts, and that their metabolites result largely from the disposal mechanisms of the liver The rapid rise in effective steroid level as doses in the physiological range are exceeded is consistent with the clinical finding that long-term side-effects increase rapidly with small increments of dosage (e g, prednisolone 7 5→10→12 5 mg)

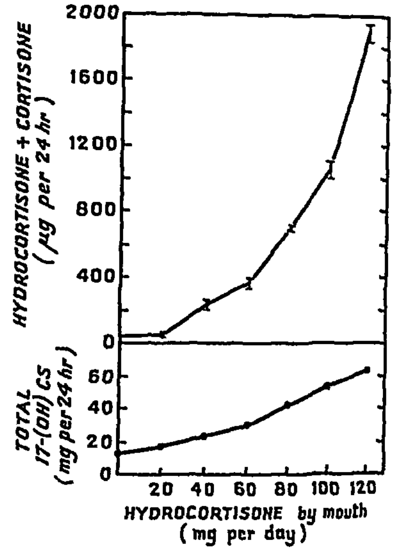

Fig 2—Increase in the absolute and relative excretion of hydrocortisone plus cortisone, and of total 17(OH)CS, at successively higher doses of hydrocortisone

An obvious criticism of urinary assays is that the findings may be upset by tubular reabsorption or excretion Since our study Schedl et al [5] have reported that 80–90% of filtered hydrocortisone is reabsorbed, and that glomerular filtration-rate and urine volume seem to have little effect This is reassuring The absolute figures given above are consistent with 80–90% reabsorption So little hydrocortisone is lost in the free form that, from teleological reasoning, one would not expect to find a purposeful selective reabsorption of hydrocortisone

We conclude that the estimation of free hydrocortisone in urine is a promising means of estimating the effective level of the hormone in the blood, and that it may well prove far more revealing than the measurement of urinary hydrocortisone metabolites

This work was made possible by research grants from the board of governors of the United Sheffield Hospitals, from the Sheffield Regional Hospital Board, and from the Nuffield Foundation

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" although a scientist may accumulate knowledge, wisdom is as difficult for him to acquire as for anyone else"
—Dr MAGNUS PYKE, *The Listener*, Jan 21, 1960, p 125

New Inventions

A BAG FOR MEASURING RESPIRATORY VOLUMES

It is often desirable to measure the vital capacity or minute volume of a patient with respiratory insufficiency, but most methods are clumsy, inaccurate, expensive, or not available at the bedside. We have used a small calibrated hexagonal plastic bag (fig 1), which is made by welding together two sheets of polyvinyl chloride (P V C) $^{10}/_{1000}$ in. (0 25 mm.) thick, and which has a P V C. inlet tube of $^{1}/_{2}$ in. (1 25 cm.) bore The obtuse angles make for easy and complete emptying, since air cannot pocket The design incorporates a wooden rod of 1 in. (2 5 cm.) diameter at the lower end. When this is rolled up the long axis, the bag becomes wrapped round it, and is therefore emptied completely A small rubber band can conveniently keep the bag rolled and ready for use When the outlet tube is occluded, the wooden rod can only be rolled partly up the length of the bag The distance from the rod to the neck, as measured by the scale on the bag, is an accurate function of the volume of gas contained (fig 2)

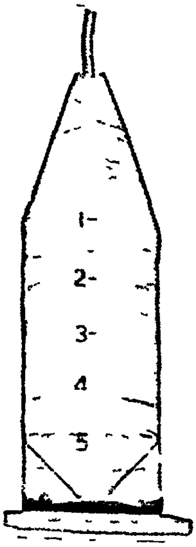

Fig 1—The bag The air compartment is outlined in black, and intermediate points on the litre scale have been omitted.

We have measured various respiratory-air volumes, and since, for example, the minute volume of expired gas from a respirator may be many times greater than the vital capacity of a severely disabled patient, we have used two bags of different sizes for different purposes The larger, which can be used for smaller volumes if accuracy is not of first importance, is 12 in. (30 cm.) wide and the smaller is 8 in (20 cm.) wide A convenient total length for each is about 24 in. (60 cm.), including tapers of 8 in. (20 cm.) at the inlet end and 4 in. (10 cm.) at the other

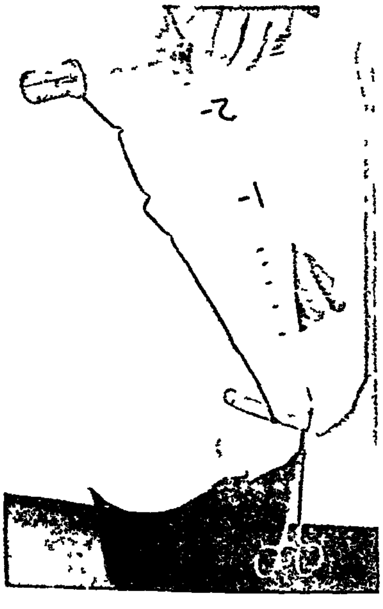

Fig 2—Measurement of a volume of about 2 6 litres. (Scale simplified for clarity)

THE BAG IN USE

The basic principle is that the observer should roll up the bag until the part containing gas is fairly tense We have found it most satisfactory first to roll the bag with both hands, and then to hold the rod in one hand and rest the bag on the other forearm, rolling until the tension feels correct (fig 2) While maintaining this degree of tension, which is arbitrary, the position of the rod on the scale should be read.

Errors may arise from variations of pressure on the gas, from various degrees of indentation of the bag, and from simple variations in reading the scale. But a series of suitably designed experiments has shown that the results are consistent for any one observer, and that the pressure to which he rolls the bag does not depend on practice. The method described above of handling the bag and reading the scale can be repeated reasonably accurately (table I) Most observations by one observer fall within the range ±2% of his mean estimate The results obtained by different observers, however, show regular differences One observer may consistently produce results whose mean is ±3% from the correct value, but such a large error is uncommon. Differences between the results obtained by various observers are largely due to differences in the pressure which they use and the compliance of the bag system. Hence if a particular observer calibrates a bag to his own method of handling, the results show a standard deviation from the mean of less than 2%, for volumes greater than 2 litres (table II)

TABLE I—TWO SERIES OF ESTIMATIONS OF GAS-VOLUME, USING THE LARGER BAG, MADE BY FOUR OBSERVERS AT 4 WEEKS' INTERVAL

Observer	*Series I* 10 observations correct value 8 47 l.		*Series II* 5 observations 4 weeks later correct value 8 67 l.	
	% error of mean	% range of errors	% error of mean	% range of errors
A	−0 83	−2 01/−0 35	−1 50	+0 3/+2 7
B	−3 30	−4 36/−0 83	−1 73	−2·0/−0 8
C	+0 12	−0 83/+1 53	−1·96	−3 1/−0 8
D	−3 18	−5·56/−0 83	−3·57	−4 3/−3 1

The observers had not used the method before the first observations nor during the 4 weeks interval.

TABLE II—ESTIMATIONS MADE BY ONE OBSERVER USING THE LARGER BAG CALIBRATED TO HIS OWN TECHNIQUE

True value (l.)	8·47	1 86
Mean of 30 estimates	8·42	1 83
% error of mean	−0 59	−1 61
% range of errors	−2·01/−3 90	−1 31/−2 69
S.D of 30 estimates about mean value (%)	1 33	1 64

The above results apply to the larger bag The smaller one can be used with similar accuracy to measure smaller volumes The shape of the taper is such that the difference between 200 ml. and 300 ml. of gas is equivalent to a distance of 1 in. on the scale

The most satisfactory method of estimating minute volume is to collect and measure the volume of gas breathed in a number of complete respiratory cycles occupying about 60 sec., timing the period accurately (Cooper 1959) [1] One can conveniently draw on the bag a nomogram from which the minute volume can be read without calculation, since, when time is represented transversely (along the axis of the rod), the rod acts as the cursor on the nomogram

These bags can be cleaned simply by rinsing, but at times they may be contaminated by viscid sputum. Satisfactory readings have been obtained with a bag in which the wooden rod is split in its long axis and held together by countersunk nuts and bolts The bottom of the bag is not sealed Thus when the rod is taken apart the bag can be opened for cleaning

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[1] Cooper, E. A *Anæsthesia*, 1959, 14 373

Reviews of Books

The Royal College of Surgeons of England—A History

Sir Zachary Cope, F R C S London Anthony Blond 1960 Pp 360 63s

The pillars of the Royal College of Surgeons have a serenity about them which makes it easy for the visitor to Lincoln's Inn Fields to realise that they have stood thus for well over a hundred years and that behind them lie the headquarters of a body whose origin can be traced back for at least four times as long He may find it more difficult to credit that, in their day, these buildings have reverberated with the efforts of the Bow Street runners to separate their dissenting occupants or that, at another time, these doors were barred, by the council of the college, against its own members

The story behind these affairs—and many more memorable and creditable activities—is here related by Sir Zachary Cope, already celebrated as surgeon, historian, and writer For this latest work he has a particular qualification, in that for nine years he was a member of the council of the college The detailed study he has now given of its evolution will be appreciated by historians everywhere—because, despite the college's venerable age and complete records, no such account has previously been published

But Sir Zachary's book is likely to find its keenest readers amongst his colleagues, the fellows and members of the college, and they will learn from it much that is likely to be new to them that when a council meeting ends, each of those who have been present throughout receive a guinea for their pains, that the Speaker of the House of Commons and the First Lord of the Admiralty are both trustees of the Hunterian Collection, and that a former president of the college once petitioned Parliament not to grant a new charter to it

Even those who have failed in their aspiration to fellowship or membership will derive some pleasure from the book, and they will certainly sympathise with the disappointed Conjoint candidate who, in July, 1920, greeted the news of his rejection by discharging a revolver six times in the Inner Hall, and threatening a college servant And any who have been tempted to condemn the court of examiners as unreasonable should note that this same candidate was given permission to present himself again, only a year later

Coronary Heart Disease

J W Gofman, M D, PH D, professor of medical physics, University of California Oxford Blackwell Scientific Publications 1959 Pp 353 60s

The author has made a distinguished contribution to the study of ischæmic heart-disease by showing that this disorder is associated with an altered physical condition of the lipids in the blood Measurements with the ultracentrifuge show increased quantities in plasma of those lipoproteins which are of low density and so can be separated and measured in a high gravitational field This change is clearly connected with the better-known rise in plasma-cholesterol also associated with the disorder From measurements of the concentrations of various components of the lipoproteins, Professor Gofman calculates an atherogenic index which he claims can be used to measure the risk of an individual to future clinical attacks of ischæmic heart-disease For some years, however, there have been claims that the atherogenic index is, at the best, an expensive substitute for a measurement of the plasma-cholesterol The evidence presented in this book is not such as to make many of the author's opponents change their minds on this point Few hospital laboratories in Britain possess an ultracentrifuge and we do not know of any convincing evidence that the need for one is strong

Much of this book is taken up with discussions of the relations of high blood-pressure, heredity, age, sex, overweight, diet, cigarette smoking, diabetes, and thyroid disease to ischæmic heart-disease These epidemiological studies are not always easy to follow on two occasions the author allows himself to run for over four pages without a fresh paragraph

Professor Gofman is an expert physicist, and there are important biophysical aspects of ischæmic heart-disease, but this book is in some ways disappointing, for one would like to know more about these aspects and less about his disagreements with the biochemists, who after all are studying the same phenomena though from a different angle

A Guide-Book to Biochemistry

Kenneth Harrison, lecturer in biochemistry, University of Cambridge London Cambridge University Press 1959 Pp 150 17s 6d (10s 6d paper-bound)

This book is intended to present the bare bones of biochemistry It aims at being useful in schools for telling pupils what biochemistry is about, and to help them to decide whether to take it as one of their university subjects It also hopes to provide an introduction for specialists in other branches of science, and for students beginning to study biochemistry

Advantage is taken of two devices a kind of shorthand which abbreviates elaborate chemical structures in capital letters, such as A T P and D P N, and " flow sheets ", whereby the pattern of complicated reactions is demonstrated by following carbon, phosphate, or chemical names through a sequence of changes without constant attention to the intricacies of chemical changes An appendix gives the formulæ of fourteen " carrier " molecules, such as A M P, A D P, D P N, T P N, and U D P G, and discusses them in detail (adenosine monophosphate, adenosine diphosphate, diphosphopyridine nucleotide, triphosphopyridine nucleotide, uridine diphosphate glucose)

Not all of the chapters, which cover energy, enzymes, oxidation, photosynthesis, carbohydrates, fat, protein, and the control of their metabolism, will be equally understood by schoolboys and non-biochemical scientists or doctors, but on the whole the author's aim is achieved In a future edition the statement that mitochondria contain the enzymes synthesising fatty acids should be corrected

Transplantation of Tissues

Vol 2 Editor Lyndon A Peer, M D, clinical and research director, Rehabilitation Center for Plastic and Reconstructive Surgery, St Barnabas Medical Center, Newark, N J Baltimore Williams Wilkins Co London Baillière, Tindall & Cox 1959 Pp 690 160s

Four years have passed since volume 1 of this large work appeared, and they have been fruitful ones for its subject A growing literature testifies to this, and one of the assets of the new volume is its comprehensive review of both new and established work It covers a much wider field than its predecessor The editor, Dr Peer (he was the author of the first volume), has twelve other contributors P B Medawar on the zoological laws of transplantation, D M. Hume on renal grafts, and Ramon Castroviejo on the cornea speak with the authority one would expect. Blair O Rogers in an interesting section on skin draws from history as well as genetics and immunology Dr Peer's own article is on fat grafts, and it will surprise most readers to find 80 pages devoted to this topic, particularly when 24 were considered sufficient for the cornea. Deterling has given as comprehensive a statement on blood-vessel grafts as could be wished for it covers the entire development of this new adjunct to vascular surgery, from the work of Carrel to the uneasy state which now prevails because of the apparent succession of cloth prostheses to the place of choice in preference to homografts Equally valuable are the sections devoted to nerve (the late Sterling Bunnell), endocrine tissue P L Krohn), and tissue culture (Mary Parshley)

This book, filled with countless carefully presented observations and the mature reflections of experts, makes it plain that transplantation still awaits its Fleming, its Banting and Best this " new dimension of accomplishment ", as Medawar puts it, is the most important subject facing surgical science today This book will have an important function in admitting more interested readers to a difficult but exciting realm of knowledge, and the guidance it gives may well add further impetus to the search for understanding

THE LANCET
LONDON 13 FEBRUARY 1960

Acute Tubular Necrosis

ACUTE tubular necrosis is the commonest cause of acute oliguric renal failure. If the patient does not die in the first few weeks of the illness, virtually complete recovery of renal function ensues,[1-3] and susceptibility to further kidney damage is apparently not increased. The management of this condition has greatly improved in the post-war years with the introduction of conservative measures to reduce the rate of clinical deterioration[4 5] and of hæmodialysis by the artificial kidney[6], and a few years ago the results of treatment were giving rise to optimism. Thus STRAUSS and RAISZ[7] wrote in 1955 "The mortality in acute tubular necrosis itself can be reduced by a combination of physiologic measures and external dialysis to nearly zero" About this time, however, reports of treatment of acute tubular necrosis in wounded soldiers in Korea[8 9] gave a less satisfactory picture. The rate of biochemical deterioration was more rapid in the traumatic cases than in the average civilian patient with little or no tissue damage. Injury to voluntary muscle was found to be especially important because there was often a rapid rise of plasma-potassium complicated by severe uræmic acidosis due to transfer of intracellular electrolytes from muscle to the extracellular fluid and plasma. Early and oft-repeated hæmodialysis was necessary, whereas non-traumatic cases could often be successfully treated by conservative measures alone. The mortality reported by TESCHAN et al.[9] in 51 wounded soldiers with acute tubular necrosis was 53%

Subsequent reports on the treatment of traumatic cases in civilian practice have been equally unfavourable. An analysis[10] of 791 cases collected from nine centres showed a total mortality-rate of 43% PARSONS and MCCRACKEN[11] report that of 25 patients with acute tubular necrosis due to complications of pregnancy or parturition only 2 died, whereas of 25 in whom the cause was accidental injury or surgical operation 18 died. BLUEMLE et al.[12] have analysed 100 consecutive cases of acute tubular necrosis treated in the University of Pennsylvania School of Medicine in the past ten years They subdivide the cases into a "favourable" group, due to transfusion hæmolysis or to obstetrical complications, with a mortality of 27%, an "intermediate" group, due to poisoning with nephrotoxic drugs or to miscellaneous causes, in which 50% died, and an "unfavourable" group, due to accidental injuries or surgical operations, with a fatality-rate of 73% A retrospective analysis of the series reported by SWANN and MERRILL[13] gave an almost identical result.

BLUEMLE et al. give a valuable detailed account of the causes of death in their cases They consider that infection was the most important single factor and that this played a major part in 72% of the fatalities Pneumonia and tracheobronchitis were the commonest types of infection, followed by intra-abdominal sepsis and septicæmia. Urinary-tract infections, which were common, did not prove immediately fatal in any patient, but in some the infection may have caused permanent renal damage. 5 patients are reported to have died from hyperkalæmia before hæmodialysis could be arranged. (This should now be a rare cause of death in advanced communities, but most centres equipped for hæmodialysis still find that patients are often transferred for treatment too late—sometimes almost moribund.) Non-infective cardiopulmonary complications and disturbances of the central nervous system, including coma and uræmic convulsions, were also of considerable importance. Excessive bleeding was troublesome, and sometimes prevented or delayed hæmodialysis As in other studies, the causes of the hæmorrhagic tendency were varied, and included reduction of blood-platelets and deficiency of several plasma-coagulation factors Delayed wound healing was another troublesome complication, and partial or complete dehiscence of abdominal incisions occurred in 5 cases In a further 6 patients fistulæ developed after abdominal operations STEIN and WIERSUM[14] have studied rupture of abdominal incisions from another angle. They found that the incidence of dehiscence in abdominal incisions in a single hospital over an eleven-year period was 0 42% The mortality-rate in these patients was 23% In all the fatal cases where adequate information was available, there was postoperative acute oliguric renal failure with severe urea retention and typical tubular lesions at necropsy.

In this week's issue Dr LOUGHRIDGE and her colleagues report on the clinical course of uncomplicated acute tubular necrosis due to obstetric and medical causes They record mortality figures similar to those in previous series and have selected the more favourable group of cases for analysis In these the course of the disease was found to be more regular and predictable, and therefore more suitable for statistical analysis, than in the cases due to trauma or surgical operations The modern tendency to restrict fluid intake to 500 ml. more than the measurable fluid loss of the previous day is shown to be an improvement on previous methods involving a more generous allowance. The average duration of the uræmia was five weeks, but at the end of this period the patients were still invalids incapable of normal activities This series should prove a useful control for a similar analysis of the more serious group

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[1] Lowe, K. G *Lancet*, 1952, i, 1086
[2] Finkenstaedt, J T, O'Meara, M P, Weller, J M, Merrill, J P *J clin. Invest* 1953, 32, 567
[3] Edwards, K. D G *Aust Ann Med* 1959 8, 195
[4] Strauss, M B *New Engl J Med* 1948 239, 693
[5] Bull, G M, Joekes A. M. Lowe, K G *Lancet*, 1949, ii 229
[6] Kolff, W J New Ways of Treating Uræmia London 1947
[7] Strauss, M. B Raisz, L. G *Arch intern Med* 1955, 95, 846
[8] Meroney, W H. Herndon, R. F *J Amer med Ass* 1954 155, 877
[9] Teschan, P E, Post R. S, Smith, L. H, Jr, Abernathy, R. S, Davis, J H, Gray D M Howard J M. Johnson K. E., Klopp, E., Mundy, R. L., O'Meara, M. P, Rush, B F, Jr *Amer J Med* 1955, 18, 172
[10] Proceedings Study Group on Acute Renal Failure C. ed by Bluemle et al (footnote 12)
[11] Parsons, F M. McCracken, B H. *Brit med J* 1959, i, 740
[12] Bluemle, L. W, Jr Webster, G D, Jr, Elkinton, J R. *Arch intern Med* 1959, 104, 180
[13] Swann R C Merrill J P *Medicine, Baltimore*, 1953, 32, 215
[14] Stein, A. A, Wiersum, J *J Urol* 1959, 82, 271

of cases with acute tubular necrosis of traumatic origin It is still uncertain whether the graver prognosis of the surgical cases is due entirely to the associated injuries and consequent increased liability to infection Possibly the injuries may prolong the uræmia either by continuing renal damage or by increasing the rate of breakdown of endogenous protein to urea and other nitrogenous waste-products

Modern Medicine in Ancient Societies

> " Too often man assumes that he can manipulate nature freely and without consequence, hence the grand effort to wipe out disease "[1]

WHEREAS immense energy goes into the application of new techniques, comparatively little attention has been paid to their secondary effects, and we are only now beginning to think seriously, for instance, about the consequences of introducing preventive and curative medicine to primitive societies In present lifetimes the material standards of most developing countries are unlikely to be raised to those of the West, yet modern medicine—or at least the lifesaving drug—is only around the corner It is encouraging to know that some of the implications of rapid medical improvement, as well as the best ways of achieving it, are now being studied by a team from Cornell University which has been working since 1952 among the Navajo Indians In a paper, based on his Jenner lecture at St George's Hospital in July of last year, WALSH MCDERMOTT et al[2] describe what is being attempted

The Navajo is the largest of the remaining American Indian tribes, and its culture is remarkably intact The population of 85,000 is scattered over a vast area (more than 23,000 square miles) of the remote south-western portion of the United States, between the Grand Canyon and the Rocky Mountains—rough country with poor communications and a climate of extremes Lively and vigorous, the tribe is based on the family and not on the village, and the family groups may be many miles from their neighbours They live in windowless mud huts with earth floors, a central smoke-hole, and no sanitation Most of the adults know no English Although there is a flourishing Navajo religion, an added difficulty for the team is the lack of any written language Sheep-farming, rug-weaving, and silver-working are the main modes of livelihood, with occasional seasonal work on the railway and farms outside the reservation MCDERMOTT emphasises the interrelation of things

> "   the Navajo stay on their ancestral land and raise sheep thus over-grazing the land so that it blows away and is subject to flash floods which make the roads impassable so that the children cannot get to school to learn English so that they cannot successfully compete in the world outside the Reservation so that of necessity they must stay at home and raise more sheep "

The Cornell group have chosen a district of 800 square miles and a population of about 2000 which returns a representative to the tribal council A preliminary survey has shown a birth-rate of 48 7 per 1000 and a crude death-rate of 7 3 per 1000 (the corresponding figures for the United States as a whole are 25 0 and 9 6)

At present, perhaps the best means of bringing medical aid to scattered homesteads in vast undeveloped areas is some form of semi-professional worker, carefully trained to advise on hygiene, perform vaccinations and inoculations, distribute simple remedies, and recognise the illnesses which require a doctor The subassistant surgeon of former days in India was such a person, and so was the old Russian feldsher, who has been retained in the Soviet medical organisation, and still does much of the medical work of the Russian countryside Less ambitiously, the Cornell group intends to use native " health visitors ", equipped with a car and radio-telephone, four of whom can be controlled by a single nurse or doctor The difficulties of course are great the need to transfer concepts from one language to another (particularly when one of the languages is not written), the influence of the traditional medicine-men (though, so far, these have always cooperated with the team), and the danger that when a person is trained in an alien technique he may become as alien as the outsider Even granted good will, enthusiasm, and supervision of the " health visitors ", there must still be risks in handing, to people of very little education, the means of life or death. As MCDERMOTT et al remark

> " With today's drugs we can place in the hands of a barefoot illiterate villager more real power to affect the outcome of a child critically ill with, say, meningococcal meningitis, pneumococcal pneumonia, or tuberculosis, than could have been exerted by the most highly trained physician of twenty-five years ago "

But some of the problems can be solved, and some have of course been tackled already in other countries In the present school year it is hoped to get virtually all the Navajo children into new schools On the precedent of South Africa, where some of the medicine-men are trained in procedures such as vaccination, perhaps some of the Navajo medicine-men could become " health visitors " Nor are the trained necessarily so alien to their own countrymen Sixty years ago an article on Russian medicine quoted a peasant from a remote district

> The doctor—oh! he's the gentleman's doctor, but the feldsher is the *moujik*'s doctor[3]

The team is studying the patterns of primitive life —in particular anxieties, diet, exercise, sleep, and the consumption of tobacco Of the diseases they have seen, some three-quarters have been due to infection (particularly streptococcal and tuberculous) and its sequels (e g , chronic otitis media) gallstones are fairly common, but cancer, hypertension, and myocardial infarction are rare (Though partly explained by the fact that few Navajo reach middle age, the rarity of myocardial infarction is remarkable, and of special interest because the Navajo diet is rich in animal fat) To illustrate how much can be done quickly, the success of an anti-tuberculosis programme may be cited

> In 1952 probably some 2–3% of the Navajo had active pulmonary tuberculosis[4] Arrangements were then made by

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[1] Gordon, J E *Amer J med Sci* 1958, 235 337

[2] McDermott, W , Deuschle, K , Adair, J , Fulmer, H , Loughlin, B *Science*, 1960, 131, 197, 280

[3] *Lancet*, 1897, ii 363

[4] Deuschle, K *Amer Rev resp Dis* 1959, 80, 200

the Government and the Cornell group to have as many as possible of these patients receive chemotherapy in the small reservation sanatorium and in sanatoria outside the reservation. In 1956 the Cornell team began ambulatory chemotherapy and the tuberculin testing of infants and schoolchildren in the project area. All positive reactors were given prophylactic isoniazid for twelve to eighteen months. As in less backward areas,[5] there was the problem of ensuring that patients took their drugs regularly.

The results from the two programmes were striking. Between 1952 and 1957 mortality from tuberculosis declined by 40%. In the project area, positive tuberculin reactions in children between 5 and 10 fell from 33% in May, 1956, to 22% two years later, while the low incidence of reactions in the school "beginners" class in the autumn of 1958 was even more significant. Of the 49 children only 8 (16%) were tuberculin-positive, and all but 2 of these were already known to be reactors. DEUSCHLE[4] regards this and the absence of miliary or meningeal disease in young children as evidence that tuberculosis is coming under control in the community.

In theory, a developing community might be able to enjoy the "best of both worlds" during the phase when the benefits of modern medicine and of traditional culture are seen together, and there are signs that this is happening to the Navajo. When this period is over, however, they will not necessarily develop the present Western pattern of disease, for, as GORDON[6] says,

> "A new influence introduced into the (ecological) system can disrupt the established balance, and set off a new succession whose ultimate end is difficult to predict."

Answers to some of the questions raised in this investigation will be applicable to developing countries outside North America. The Navajo microcosm, situated inside the richest economy in the world, cannot accurately represent the macrocosms of present-day Asia and Africa, but they have many things in common. In particular, the possibility of real harm from too rapid or too enthusiastic technological change must never be forgotten anywhere. McDERMOTT quotes Mr GEORGE KENNAN:[7]

> "Wherever the authority of the past is too suddenly and too drastically undermined—wherever the past ceases to be the great and reliable reference book of human problems—wherever, above all, the experience of the father becomes irrelevant to the trials and searchings of the son—there the foundations of man's inner health and stability begin to crumble, insecurity and panic begin to take over, conduct becomes erratic and aggressive. These, unfortunately, are the marks of an era of rapid technological or social change."

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[5] Dixon, W. M., Stradling, P., Wootton, I. D. P. *Lancet*, 1957, ii, 871.

[6] Gordon, J. E. *Amer. J. med. Sci.* 1958, 235, 341.

[7] Kennan, G. Realities of American Foreign Policy. Princeton, 1954.

Annotations

PRIVATE PATIENTS IN THE NATIONAL SCHEME

THE Government are being strongly pressed to allow practitioners to prescribe National Health Service drugs for their private patients. The case is arguable, and it is argued with conviction by many who believe in revival of private practice as a remedy for current ills. Everybody, indeed, must see something harsh in a system which says that, because a person prefers to get his medical help from a doctor outside the National Health Service, or to consult an N.H.S. doctor privately, he cannot have the medicines which, as a taxpayer, he has helped to provide.

The British Medical Association has long maintained that he ought to have them, but it recognised that safeguards would be required before purely private doctors could distribute public property. Accordingly, in December, 1958, it agreed that private patients wanting to use N.H.S. drugs should be registered on a list with the local executive council, and that, in respect of them, private doctors would submit to the same code of conduct and penalties as apply to their N.H.S. colleagues. Unfortunately, simple though this solution sounds, it is not really simple at all. For, though the doctors concerned might continue to think of themselves as private, they would in point of fact be entering the Health Scheme—and entering it without accepting payment by capitation. Even though the patient would be paying his doctor privately, the arrangement would amount to Government recognition of the fee-for-service system.

For our part we trust that, before acting on such a plan, the Government will look at more than its financial implications. Much importance has rightly been attached to the principle that, within the National Health Service, medical privileges cannot be bought. (The apparent exception—the private bed in a hospital—is not really an exception at all: the patient in a pay-bed is paying at least the full cost of his treatment, and, though the bed, with services, are rented to him by the N.H.S., he is in fact being treated at his own cost by his own doctor, outside the service.) The proposal now made is that, *within* the national scheme, patients, by paying fees, shall be able to buy the doctor's time, and the convenience of access to him, which are so important a part of good personal care. Since the commonest criticism of N.H.S. general practice today is that it often fails to provide these things, a great many people might be willing to buy them. Yet we all know that good personal care ought to be provided for everybody who needs it—not sold. Surely the last thing we should now do is to establish within the service a group of people who are engaged in selling care of a higher standard, and who therefore have a vested interest in preserving the defects of ordinary medical care? What we need to do, on the contrary, is to give all practitioners a vested interest in getting rid of those defects.

If the capitation system of payment is really a bar to the necessary improvement, let us change it. But whatever else we decide on, do not let us have within the national scheme two levels of medical attention—a new and better one for those who consult their doctor privately, and another for those who do not.

STEROIDS AND ECZEMA

DERMATOLOGISTS can count among their blessings the accessibility of the skin, which enables them to paint, anoint, or spray their patients with steroids. The effectiveness of these measures in many cases of eczema is manifest, and Nordin,[1] who has studied the toxicity of steroids, advises dermatologists to content themselves with topical application whenever possible. It would be premature, however, to assume that topical application never carries a risk, though it is clearly safer than systemic treatment. Nordin found up to 8% mortality attributed to systemic steroid treatment in 11 reported series, one of which[2] concerned 200 patients who suffered from a wide variety of dermatoses including pemphigus, of whom 22 had serious complications and 7 died But the significance of these findings is doubtful, since no distinction was made between those on high life-saving doses and those on small suppressive ones

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[1] Nordin, B. E. C. *Brit. J. Derm.* 1960, 72, 40.

The lives of patients on systemic steroid treatment are threatened in various ways[3] their gastrointestinal tracts may perforate or bleed they are prone to intercurrent infections, whose symptoms are masked, or to recrudescence of latent infection, they are probably particularly susceptible to thromboembolic catastrophes, and they are liable to a number of other potentially serious complications In view of this catalogue of iatrogenic disaster and suffering it is natural that Cronin and Wells[2] were extremely reluctant to treat with systemic steroids atopic eczema (Besnier's prurigo), which is not a fatal disease Nevertheless Sneddon[4] felt from his experience that the dangers of suppressive doses might have been exaggerated He has given steroids to 26 patients with atopic eczema, selected from 500 for their severity, their failure to respond to other treatment, including topical steroids, and their freedom from tuberculosis, hypertension, and dyspepsia The treatment has continued for periods of up to 4¹/₂ years, and the daily maintenance dose was usually between 5 and 15 mg of prednisolone In 19 patients the result was good and in 5 fair No serious complications arose, but most patients have become plumper Infection or emotional stress required a temporarily increased dose of steroid, and the risks of surgery have been partly met by issuing a warning card to all patients and urging them to produce it if they consult a surgeon

The patients improved in personality and coped with life more easily, a change reflecting perhaps the great influence of the dermis on the psyche, as well as the heavy burden of cutaneous misery which such patients carry Lamont,[5] who reported a somewhat similar series, concluded that the prospect of having to continue treatment indefinitely might make the physician prefer other measures But it seems that this method might well help selected patients with atopic eczema as nothing else could If further study confirms its good effects and comparative safety it could truly be said that the disease was worse than the effects of suppressing it Until then it would be wise to remember Sneddon's final sentence " some harmful effects may yet arise and treatment should not be embarked upon lightly or in the absence of adequate facilities for close supervision "

COLD-FOOT SYNDROME

THE typical pain of myocardial infarction may be overshadowed by syncope, shock, vomiting, or dyspnœa, but Wood[6] believes that only 5% or less of patients who are carefully questioned deny the presence of pain or some oppressive sensation in the chest during the acute attack, and Roseman[7] could discover only 5 entirely painless infarcts in a series of 220 patients On the other hand the observations of Stokes and Dawber[8] and of Weitzman and Smith[9] show that myocardial infarction can apparently occur without any symptoms and be completely silent Infarcts complicating surgical operations are particularly liable to be overlooked[10,11] because pain is often suppressed by anæsthesia or analgesic drugs,[12] and the picture may be one of shock or persistent hypotension

Frank[13] has described the syndrome of " cold foot ", which may be the presenting sign of an otherwise silent postoperative myocardial infarction According to Frank the discovery in the postoperative period of a cold foot on one side, often numb or painful, associated with absent arterial pulsation and with ischæmia on elevation, almost invariably indicates myocardial infarction if the heart rhythm is normal and murmurs are absent The syndrome is, of course, the consequence of arterial embolism in the leg, and, as Haimovici[14] has shown, the vast majority of emboli originate in the heart less common causes are dislodgment of atheromatous aortic plaques, thrombi arising in the pulmonary veins, and, very rarely, paradoxical embolism through a septal defect Primary arterial thrombosis is unlikely unless there is pre-existing vascular disease in the lower limbs Consequently if atrial fibrillation, rheumatic heart-disease, or bacterial endocarditis can be excluded, recent myocardial infarction is the probable cause Frank has detected the syndrome in 3 patients, 5, 7, and 13 days after abdominal operations in all 3, electrocardiography confirmed recent infarction Like Wasserman et al[12] he believes that anæsthesia or postoperative analgesics may prevent appreciation of the pain of myocardial infarction, but he also points out that when pain is felt it may be wrongly attributed to the discomfort of an abdominal wound

THE ALBEMARLE REPORT

THE fundamental and inescapable conflict in teenagers stems from the fact that biological maturity is reached so much sooner than social fulfilment There is nothing new in this What is new is the influence of the changing pattern of our culture—especially the mass media of communication The resulting strains have thrown into relief the difficulties of the years of transition The challenge to society is full of opportunities

Enthusiasm runs through the fascinating report of the Albemarle Committee,[15] published last week This committee was set up by the Minister of Education in 1958 with the following terms of reference

> " To review the contribution which the Youth Service of England and Wales can make in assisting young people to play their part in the life of the community, in the light of changing social and industrial conditions and of current trends in other branches of the education service, and to advise according to what priorities best value can be obtained for the money spent."

In critical terms the report notes the failure of successive Governments to provide the means of bringing the youth service properly to life Reaching only one teenager in three its chief strength has been voluntary help In 1957–58 for each £1 the Government spent on education only 1*d* was available for the youth service Small wonder that its development has been haphazard and that its present condition gives rise to anxiety Whether or not it is " dying on its feet " the committee acknowledges that it is " in a state of acute depression " To the diffi-

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culties caused by lamentably inadequate money, drab and unimaginative premises, and a catastrophic shortage of adult helpers with the right training and outlook have been added the effects of "the bulge", the ending of National Service, and the social significance of young people with £3 or more spending money a week in their pockets. Against this background, and aware of a "new climate of crime and delinquency", the committee proclaims and justifies a belief in the immense contribution a youth service can make. This contribution can be made only if the service is expanded and continuously nourished: meanwhile we must rely on short-term, emergency "blood-transfusion" methods.

The four great needs are an imaginative and vigorous approach, money, greatly improved premises, and a large increase in trained workers. The committee proposes the establishment of a Youth Service Development Council, numbering not more than a dozen, to advise and help the Minister. A ten-year development programme, starting this year, is recommended; the first half would be devoted to catching up with events, and the second to establishing a permanent structure on firm ground. Local education authorities are recognised as having a crucial role in the growth of what, after all, is part and parcel of full education for living. Arrangements for providing the necessary leaders are considered in detail. A proposed emergency training college would increase the present force of 700 full-time leaders to a provisional 1300 by 1966. Part-time workers, both paid and voluntary, clearly have an important part.

If these recommendations are implemented there will be real grounds for hoping that the needs of the young generation can be met constructively. Implicit in the committee's approach is the conviction that the Government really does intend to make the youth service adequate, and the Government's acceptance of the main proposals is encouraging.

PSEUDOMONAS AND POLYMYXIN

ONLY a concerted hospital policy, such as that initiated by Barber and her colleagues[1] at Hammersmith Hospital, is likely to stem the increase of resistant strains of staphylococci in our hospitals. The shadow of a further danger—an increased incidence of gram-negative infections, particularly with *Pseudomonas pyocyanea*—was cast by the results of the twenty-two-year survey conducted by Finland and his colleagues at the Boston City Hospital,[2] where there has been a sixfold increase in gram-negative septicæmias since the introduction of antibiotics. The situation is similar in British hospitals, as is pointed out on a later page of this issue by Dr Roger Williams and his coworkers, who noted an upsurge of *Ps pyocyanea* infections in Hammersmith Hospital during 1959. Whereas in the first quarter of 1958 only 9 patients were known to have this organism in their sputum, it was found in the sputum of more than 60 patients during a similar period in 1959. In one general medical ward pseudomonas infections were responsible for 5 deaths, and, in addition, sporadic cases of localised infection and of septicæmia arose throughout the hospital. Poor resistance undoubtedly contributed to the 5 deaths, for 2 patients were leukæmic, 1 had agranulocytosis, another was in respiratory failure, and the 5th was receiving long-continued oral corticosteroids on account of hæmolytic anæmia. But Williams et al. suggest that the increase may also be related to the doubled consumption of tetracycline and other broad-spectrum antibiotics.

The only antibiotic that combats pseudomonas infection really effectively is polymyxin. This was isolated independently in Britain[3] and in the United States[4,5] from *Bacillus polymyxa*, and in this country was originally known as 'Aerosporin' (its present trade name.) It is now available as polymyxin B sulphate powder in vials containing 500,000 units. It may be given by mouth and by intravenous, intramuscular, intrathecal, subconjunctival, and intrapleural routes. There are various topical preparations, and a 0.1 to 1.0% saline solution may be used to irrigate sinus tracts. Polymyxin, which is not absorbed from the gut, may be given by mouth for bowel infections which do not respond to sulphonamides, streptomycin, or neomycin. Since it does not affect the gram-positive intestinal flora, monilia and other fungi do not emerge as dominants. For systemic infections, it is administered intramuscularly in a dose of 20,000 units per kg daily, an average dosage for adults being 250,000 units four-hourly. Because of pain at the site of injection, it should be administered with procaine and the site frequently changed. During treatment with polymyxin, the urine should be examined daily for albumin and casts, and the blood-urea level should be estimated twice weekly as the drug is potentially nephrotoxic. The indication for its use in severe infections that resist other antibiotics usually outweighs the risk of toxicity. This risk has hitherto prevented its widespread use: which can now be counted as a blessing, for otherwise *Ps pyocyanea* might not be still sensitive to the drug. Polymyxin should on no account be used for the treatment of trivial hospital infections.

CONGENITAL MALFORMATIONS

FROM many sides, the pathogenesis, the possible prevention, and the treatment of congenital malformations are getting more and more attention: as postnatal infections come under control, what has been called prenatal pædiatrics is gaining in relative importance. The time is ripe therefore for the first International Congress on Congenital Malformations, and we are glad that it will be held here in London next July.

The honorary presidents are to be the Hon. Basil O'Connor and Sir Geoffrey Marshall, and the general chairman Prof. J. D. Boyd, of Cambridge. Meeting at Church House, Westminster, on July 18, the congress will have a theme address from Dr George W. Corner, and will spend five days on sessions entitled: Incidence, Intrinsic Factors (genetics), Extrinsic Factors (environment), General Developmental Mechanisms, Abnormal Developmental Mechanisms, Maternal-Fœtal Interactions, Physiological and Medical Problems, and Perspectives. The executive secretary and treasurer of the congress is Mr Stanley E. Henwood, and his office is at 67, New Bond Street, London, W.1.

The report of the Royal Commission on Doctors' and Dentists' Remuneration will be published on Feb. 18.

Prof. E. J. WAYNE has been appointed chairman of the clinical research board of the Medical Research Council in succession to Sir Geoffrey Jefferson, who has retired after a six-year term of service as first chairman of the board.

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Special Articles

CROSS-INFECTION WITH PSEUDOMONAS PYOCYANEA

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Pseudomonas pyocyanea is well known as a relatively avirulent secondary contaminant of superficial wounds and burns, but more serious infections may occur, particularly in infants or in adults whose resistance is weakened by other disease This organism tends to be resistant to the commonly used antibiotics, and with the widespread use of these agents there is some evidence that the incidence of infection with *Ps pyocyanea* is increasing

Yow (1952) traced 56 examples of infection due to *Ps pyocyanea* or proteus during or following antibiotic therapy over a two-year period On analysing the routine cultures received in the bacteriology department during this time he found that the incidence of *Ps pyocyanea* had risen from 15% of the gram-negative bacilli isolated to 30% In children with mucoviscidosis Garrard et al (1951) observed that the decrease in frequency of staphylococcal infections was accompanied by an increase in those due to *Ps pyocyanea*

During the past year we have experienced in this hospital a disturbing incidence of cross-infection with *Ps pyocyanea*, and we draw attention here to some of the problems involved In one general medical ward alone, pseudomonas infection was responsible for 5 deaths These are described together with studies of the probable source of infection and mode of transmission

Case-reports

Only a brief account of the clinical course is given as the main bacteriological and pathological findings are shown in table I

Case 1.—A man of 22 was admitted in May, 1958, with acute leukæmia After three weeks' treatment with 6-mercaptopurine the white-blood-cell count had fallen to 1800 per c.mm. (polymorphs 5%) He then developed a fever up to 104°F and signs of bronchopneumonia, the sputum growing *Ps pyocyanea* in pure culture There was no response to antibiotics (including streptomycin) and he died three weeks after the onset of fever

Case 2.—A man aged 54 was admitted in July, 1958, with polyarthritis, fever, and agranulocytosis, this last being attributed to phenylbutozone which he had been given two months earlier Although the arthritis responded to salicylates the fever continued, and a chest X-ray showed pneumonic shadowing in the left upper zone There was some response to antibiotics (penicillin and streptomycin) and prednisolone, but when the antibiotics were discontinued the fever recurred. Finally at the beginning of August numerous papular skin lesions appeared over the trunk and limbs, many of them became nodular with dusky red hæmorrhagic centres increasing in size up to 1 in in diameter At this stage *Ps pyocyanea* was isolated The patient died on Aug 10, three weeks after admission.

Case 3—A 59-year-old man, a known case of chronic lymphatic leukæmia, was readmitted in October, 1958, with acute cholecystitis The white-cell count on admission was 4000 per cm (polymorphs 10%) His symptoms subsided rapidly with antibiotics (tetracycline and erythromycin) but he then developed a sore throat followed a few days later by pseudomonas septicæmia This responded initially to streptomycin, but later the fever recurred and laparotomy was performed This revealed an empyema of the gallbladder which was drained, but the fever continued and despite systemic polymyxin he died three days later

Case 4—A man of 50 with a long history of chronic bronchitis and emphysema was admitted in December, 1958, with an acute exacerbation After an emergency tracheostomy and bronchial aspiration treatment was continued with intravenous hydrocortisone and antibiotics (penicillin and streptomycin) He improved dramatically at first but on the morning of the third day after admission his temperature rose to 104°F *Ps pyocyanea* was now present in the sputum, and he died later the same day

Case 5—A man, aged 79, with acquired hæmolytic anæmia had been maintained on prednisolone (20 mg daily) since June, 1957 He was readmitted in September, 1958, with fever and a mass in the right lung presumed to be a carcinoma He was treated with radiotherapy and antibiotics (tetracycline and novobiocin) but developed pseudomonas diarrhœa This did not respond to neomycin, and profuse watery diarrhœa persisted until his death in peripheral circulatory failure on Dec. 11

MICROSCOPICAL FINDINGS

The histological appearances of the septicæmic lesions in the first 3 cases were basically similar with an area of central necrosis, in which traces of pre-existing structure remained, surrounded by a narrow inflammatory zone

TABLE I—BACTERIOLOGICAL AND PATHOLOGICAL FINDINGS IN 5 FATAL CASES OF PSEUDOMONAS INFECTION

Case no	Pseudomonas cultures during life							Necropsy cultures (pseudomonas)	Relevant postmortem findings
	Specimen	Antibiotic sensitivity pattern							
		P	STR	T	C	N	Poly		
1	Sputum	R	R	R	R		S	Liver, lungs, kidneys	Multiple small septic infarcts in liver, lungs, and kidneys
2	Blood Skin biopsy	Not done "						Lungs	Multiple firm nodules in lungs, small abscesses in kidneys, *multiple skin nodules*
3	Throat swab		S		R		S	Pus in paracolic gutter	Acute cholecystitis, peritonitis, small abscess in prostate, multiple small nodules in pleura, and two larger ones in right upper lobe
	Blood (1st episode)		S				S		
	Blood (2nd episode)		R	R	R	S	S		
	Empyema pus		R	R	R	S	S		
4	Bronchial aspirate	R	R	R	R		S	Right lung	Acute bronchitis, confluent bronchopneumonia on right side
5	Stool		R		R	S	S	Not done	Numerous yellow ulcers up to 0 8 cm in diameter throughout large intestine

P = penicillin. STR = streptomycin. T = tetracycline C = chloramphenicol N = neomycin Poly = polymyxin. R = resistant. S = sensitive

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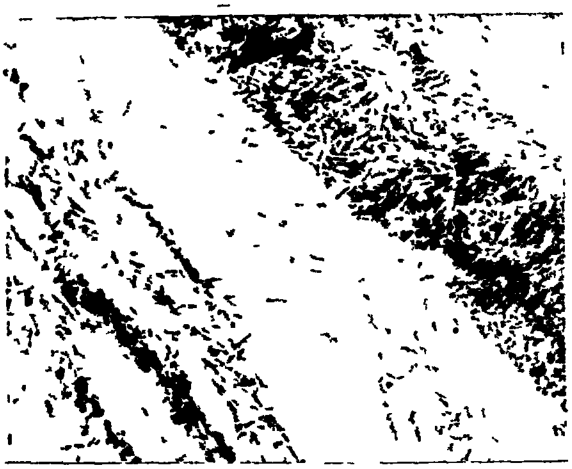

High-power view of the wall of an artery adjacent to a pulmonary lesion in case 1 Innumerable bacilli are seen in the artery wall, and small numbers are present in the antemortem thrombus in the dilated lumen (lower left) (Acid fuchsin/picric acid ×950)

containing relatively few polymorphs and much granular debris Gram-negative bacilli were present in the periphery of the lesions and were also seen in very large numbers in the walls of adjacent small arteries (see figure) Some of these were occluded by antemortem thrombus, and in the 1st case a small mycotic aneurysm was found near one of the pulmonary foci The skin nodules in case 2 showed a similar histological picture to the visceral lesions, and numerous bacilli were present in the wall of an adjoining artery The lung lesions in case 3, though similar in distribution and histological structure to those in the first 2 cases, did show some surrounding fibrosis, and it seems likely that these were the result of a previous septicæmic episode (particularly as shadows corresponding to the site of these had been noted in a chest X-ray taken six months before death when the patient was admitted with pyrexia of unknown origin)

In the other 2 cases there was no evidence pathologically of septicæmia In case 4 the bronchopneumonia was remarkable on microscopy for the poor cellular reaction and the numerous gram-negative bacilli in the alveolar exudate Similarly in case 5, despite the widespread ulceration, there was only a slight cellular reaction consisting mainly of plasma cells

Sources of Infection

Infection with *Ps pyocyanea* was not restricted to this one ward, and sporadic cases both of localised infection and of septicæmia occurred throughout the hospital during the year We have described only those cases occurring in the one ward as more information is available there regarding the mode of transmission and possible sources of infection

It seems likely that infection was airborne, for bacteriological studies showed a high concentration of *Ps pyocyanea* in the air Also pneumonic signs were present at an early stage in cases 1, 2, and 4—suggesting a portal of entry via the respiratory tract, and in case 3 the organism was first demonstrated in a throat swab In keeping with this mode of transmission the main source of infection appeared to be sputum Table II shows details of all the patients in the ward during the year who had sputum from which *Ps pyocyanea* was isolated These were mainly cases of chronic respiratory disease, and the organism appeared in the sputum as they were improving clinically after a course of broad-spectrum antibiotics 4, however, had not been treated with antibiotics Although in these the organism was cultured from the first specimen examined, this had not been sent until several days after admission, so the infection may well have been acquired in the ward It can be seen from table I that apart from February, March, and April there were always one or two patients in the ward with sputum containing *Ps pyocyanea* The first of the patients who died later of pseudomonas septicæmia was admitted soon after a patient with bronchiectasis whose sputum consistently yielded a heavy growth of this organism

It is apparent from the varying antibiotic sensitivity pattern of the organisms isolated (tables I and II) that the infections both in the fatal cases and in the patients with respiratory disease could not be attributed to a single strain and probably several were involved.

Discussion

The first 3 cases show many of the distinctive clinical and pathological features of pseudomonas septicæmia. Although in case 1 a positive blood-culture was not obtained in life, there were at necropsy widespread septicæmic lesions from which *Ps pyocyanea* was cultured in pure growth Fraenkel (1917) originally stressed the tendency of this organism to multiply in the walls of small blood-vessels, producing acute inflammatory arteritis Secondary thrombosis leads to arterial occlusion and the formation of small infarct-like areas of necrosis, which were such a striking feature of the present cases Characteristic skin lesions may occur in pseudomonas septicæmia and may be of help in early diagnosis These (as in case 2) begin as macules or papules and later form round indurated areas with black necrotic centres from which the organism

TABLE II—DATA ON ALL THE PATIENTS IN THE WARD DURING THE YEAR WHO HAD SPUTUM FROM WHICH *Ps Pyocyanea* WAS ISOLATED

Patient	Diagnosis	Present on admission	Date first isolated	Previous antibiotics	Growth	Antibiotic sensitivity pattern					
						P	STR	T	C	Poly	Sul.
A	Chronic bronchitis	No	Jan. 13	Chloramphenicol	++		R	S	S		
B	Bronchiectasis	No	May 14	Penicillin, chloramphenicol, tetracycline	+++	R	S	R	R	S	R
C	Leukæmia	No	June 16	Tetracycline and novobiocin	++	R	R	R	R	S	S
D	Lung cancer		June 23	None	+		S	R	R		
E	Chronic bronchitis		July 12	None (during this admission)	++		S	R	R	S	
F	Lung abscess	No	Aug 7	Tetracycline and novobiocin	++		S	R	R	S	
G	Chronic bronchitis	No	Sept. 9	Novobiocin and chloramphenicol	+++		S	R	R	S	
H	Mitral stenosis		Sept. 9	None	++		S	R	R	S	
I	Lung abscess	No	Oct. 11	Erythromycin and novobiocin	+	R	S	R	R	S	R
J	Asthma		Oct. 18	None	+−−		S	R	R	S	
K	Chronic bronchitis	No	Oct. 22	Chloramphenicol and novobiocin	++−			R	S		
L	Lung cancer	No	Nov 11	Tetracycline and novobiocin	+++		S	S			
M	Cardiac infarction		Nov 19	None	+		S	R			
N	Pneumonia		Dec. 5	Penicillin streptomycin chloramphenicol	++	R	R	R		S	
O	Bronchiectasis	No	Dec. 15	Tetracycline and novobiocin	+−		R	R	R	S	R
P	Chronic bronchitis	No	Dec. 31	Tetracycline and sulphonamide	++		R	R	R	S	S

P=penicillin. STR=streptomycin. T=tetracycline. C=chloramphenicol. Poly=polymyxin. Sul.=sulphonamide. R=resistant S=sensitive can easily be cultured In a recent series of 23 cases of pseudomonas septicæmia (Forkner et al. 1958) skin lesions were present in 9

In the other 2 cases the infection remained localised and bloodstream invasion did not occur In case 4 secondary infection with *Ps pyocyanae* was probably responsible for the clinical deterioration after the earlier response to treatment In case 5 the severe diarrhœa undoubtedly contributed to death Although *Ps pyocyanea* may be isolated occasionally from routine stool cultures, the number of organisms is small and, in those cases where tissue invasion occurs with ulceration of the mucosa, as in this patient, large numbers are seen, at times as many as 50-75% of the colonies isolated are of this organism (Stanley 1947)

Each case had previously been treated with broad-spectrum antibiotics This is in keeping with the role of *Ps pyocyanea* as a secondary or superinfecting organism Forkner et al (1958) found that 77% of pseudomonas septicæmias occurred in patients receiving broad-spectrum antibiotics, whereas only 33% of those due to staphylococci occurred under such circumstances. Experimentally, in mice both cortisone and radiation increase the susceptibility to pseudomonas septicæmia (Ross 1956, Millican et al 1957), and there is suggestive evidence in man that anti-metabolite administration may be another predisposing factor (Forkner et al 1958) All our cases had received corticosteroids, and case 1 and 3 antimetabolites, although in case 3 this was many months previously

The occurrence of a normal or low white-cell count in both localised and bloodstream infections with *Ps pyocyanea* has been recognised since 1899 when Ghéorghiewsky claimed to have found a leucocyte-destroying ferment in cultures of this organism and Brill and Libman remarked on the absence of leucocytosis in 2 cases of pseudomonas septicæmia Later, several workers (Lovett 1924, Linthicum 1927, Dasse 1928) isolated this organism from the local lesions and occasionally from the bloodstream of some cases of agranulocytic angina and showed experimentally in guineapigs that it had a direct lytic effect on leucocytes and possibly also an inhibitory effect on their formation in the bone-marrow On the other hand, patients with low white-cell counts are abnormally susceptible to infection and may be particularly liable to pseudomonas septicæmia Forkner et al (1958) found that *Ps pyocyanea* was the most frequent bacterial cause of death in leukæmia and the second most frequent cause of septicæmia Many factors other than a low polymorph-count may, however, contribute to the diminished resistance in acute leukæmia, including abnormal antibody response and altered phagocytic properties of the leucocytes (Silver et al 1960) 2 of our patients had leukæmia and the 3rd marrow asplasia probably secondary to phenylbutazone toxicity, and in all 3 the neutropenia preceded the septicæmia In a fatal case of pseudomonas septicæmia recently in one of the surgical wards, the white-cell count dropped to 2200 per c mm on the fourth postoperative day, but by the time of death, two days later, it had risen to 8000 per c mm

The high mortality of pseudomonas septicæmia is of course related as much to the underlying disease as it is to the superimposed infection All but 2 of the 22 fatal cases reported by Forkner et al (1958) had malignant disease Other series which include cases with less serious underlying disease have a lower mortality (Martin et al 1954) The majority of strains of *Ps pyocyanea* are sensitive only to polymyxin or neomycin Unfortunately, both these drugs are toxic when administered parenterally, although if careful attention is paid to dosage this risk can be largely averted Jawetz (1952) used polymyxin B in a dose of 2 5 mg per kg body-weight for six days in 35 patients with pseudomonas infections over a two-year period without any nephrotoxic effects, but even when this drug is given in pseudomonas septicæmia the result may be disappointing In the series reported by Forkner et al (1958) 9 cases were treated with polymyxin but none improved although in 3 the blood-culture became negative Occasional strains are also sensitive to streptomycin, but resistance usually develops rapidly as in case 3 of the present series

There seems to be no doubt that the patients reported here acquired their infection after admission to hospital Little attention has previously been paid to the problems of cross-infection with this organism in medical wards Forkner et al (1958) studied the incidence of septicæmia in 13 patients with leukæmia treated in the same unit over a twenty-month period They found that septicæmia due to *Ps pyocyanea* tended to occur in small groups in contrast to the random distribution of other bacterial septicæmias, though the factors responsible for this were not clear In an outbreak of infantile diarrhœa in a children's ward (Florman and Schifrin 1950) indirect spread via nursing staff was thought to have occurred as the organisms were isolated from the hands of two nurses who shortly before had handled children with positive stool-cultures An airborne mode of transmission was considered likely in a series of cases of pseudomonas meningitis and penetrating head injuries reported by Botterell and Magner (1945) as a high concentration of *Ps pyocyanea* was found in the air of the wards, all of which were over-crowded

The importance of sputum as a reservoir of infection with *Ps pyocyanea* is shown by the present studies The appearance of this organism in the sputum of the majority of the patients, described in table II, was not accompanied by any clinical signs of infection Nevertheless, it is probably from these patients that the more serious infections in susceptible subjects originate They constitute in this hospital a serious and increasing problem In the first quarter of 1959 there were more than 60 patients with *Ps pyocyanea* in their sputum, whereas during a similar period of 1958 there were only 9 It is tempting to relate this increase to the greater use of tetracycline and other broad-spectrum antibiotics, the consumption of which has nearly doubled over the past year

Various measures may help to prevent cross-infection Clearly the use of broad-spectrum antibiotics should be limited as far as possible. Patients with this organism in their sputum should be taught to cough directly into a sputum pot containing a suitable disinfectant such as ' Sudol ' which has the same bactericidal spectrum as ' Lysol ' without its irritant effect Treatment with inhalations of polymyxin (25,000 units) and neomycin (5 mg) given four times a day through a Wright nebulizer is sometimes followed by disappearance of the organisms from the sputum, but in our experience systemic polymyxin is necessary in those with a heavy growth Ideally these patients should be isolated, but this has proved difficult owing to the numbers involved A more practical measure is to isolate patients with leucopenia from any cause, who appear to be particularly at risk from cross-infection with *Ps pyocyanea*

Summary

Cross-infection with *Ps pyocyanea* materially contributed to 5 deaths in one ward in 1958

Predisposing factors appeared to be a low white-blood-cell count and previous treatment with corticosteroids and broad-spectrum antibiotics

The infection was apparently airborne, and the main source was the sputum of certain patients with chronic respiratory disease

The frequency of infection with this organism is increasing

We would like to thank Dr J G Scadding and Dr P Hugh-Jones under whose care these patients were admitted for permission to publish this report We are indebted to Mr J Griffin and Miss G Fisher for histological assistance, and to the bacteriology department for help and particularly to Dr Mary Barber for advice and encouragement

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PRESERVATION OF MEDICAL RECORDS

A Memorandum by the British Records Association [*]

THE medical profession is uncomfortably familiar with the proliferation of papers which modern methods of office administration produce. The resulting accumulation of papers too often provokes periodic indiscriminate destruction, in which records of value and interest, often of some age, may disappear, along with masses of modern ephemeral material To avoid the ill-effects of unregulated destruction the Association has published memoranda stating general principles for the disposal of records such as are described in its Memorandum no 7, *Modern Records, what may we destroy?*

Since the National Health Service was instituted, certain classes of medical records—e g , those of hospitals and hospital administration—come under the control of the Minister of Health and are subject to the statutory arrangements for public records The Ministry issues directions about their preservation and destruction, which are drawn up in consultation with the Public Record Office The medical records accumulated in health departments of local authorities will, in general, be covered by the arrangements existing within each authority for the preservation of departmental records The following advice is, therefore, primarily directed to individual practitioners, voluntary hospitals, and other organisations or persons whose records are not covered by the preceding arrangements

Records may be classed for the purpose of preservation as those of the distant past, those of the immediate past, and present-day records A convenient division between the distant and immediate past is afforded by the Medical Act, 1858, before which no compulsory system of registration of medical practitioners was enforced. Present-day records may be regarded as beginning with the National Insurance Act, 1911 All records before 1858 should be kept and none of those relating to the period 1858–1911 should be destroyed before advice has been obtained. As regards documents later in date than 1911, the pamphlet *Modern Records, what may we destroy?* provides, in general, adequate guidance There are, however, two kinds of record which call for special consideration.

First, there are the records of individual doctors Details of how practices were run, how patients were referred to the doctor, how many he saw in a day, &c., are very difficult to find. Therefore visiting-list books, letters giving details of consultations, and diaries containing professional rather than personal matters, should be looked for and, if possible, preserved. They are, in general, the kind of thing that tends to be destroyed as being apparently of no interest.

Then there is the clinical note, a kind of record peculiar to medicine, of which, over the years, there may be such accumulation that their preservation in entirety is a matter of some difficulty [†] But there are special reasons why case-notes *are* of historical value They are, for instance, the best source for the history of the introduction of the physical examination of patients and of other methods of investigation, of the invention and applications of pathological investigations, such as the chemical testing of urine, of the introduction of bacteriological principles into medical consciousness, and of the development of radio-diagnosis and the introduction of radiotherapy Case-notes also provide a far more accurate basis for the history of treatment than do textbooks, because they tell what was in fact given to patients, and not what was recommended Some historical matters (such as the rise and fall of the use of arsenic in internal medicine) would be impossible to elucidate without original records They also provide first-hand evidence of the changing attitude of doctors to disease at different times, and contain a great deal of intimate detail about habits, food, drink, clothing, housing, and families of patients Case-notes, therefore, constitute a very accurate and impartial record of social history There are thus many sound reasons for their preservation as far as is practicable.

It may be physically impossible for the organisation which produces case-notes or other medical records to provide permanent storage for all of them, but every effort should be made to preserve them The use of scarce office space for the storage of these records may be difficult to justify, but the attic, roof space, or cellar, will provide an alternative " limbo " If these records can be kept, in whatever order and state (damp excepted), they will at least exist and still be available for the painstaking searcher who desperately needs them.

By their nature, medical records, especially clinical records, are highly confidential, and before allowing them to leave their possession, practitioners and institutions will certainly wish to be assured that this confidential nature will be respected. Certain standard conditions of receipt by archive repositories should attach to accessions of medical records for the protection of all parties In general, no clinical records should be available for public inspection until a hundred years after the date of the last entry This term could be varied at the discretion of the archivist in the case of a person conducting bona-fide research on production of evidence of his standing and competence In no case should names of patients be quoted, and individual cases should not be identified by name in any work published as a result of such research, until after the passage of a hundred years Persons consulting medical records should be required to give a signed undertaking to observe these conditions before being allowed access to the information. A general condition of deposit in the case of clinical records or case-books would be that those records would only be opened to members of the public subject to the above restrictions Any lists of the records compiled in the archive repository and placed on open access shelves in search rooms should bear clear statements of these restricted terms of access It is felt that such conditions, if clearly explained to practitioners and institutions before a deposit were made, would satisfy them that the confidential nature of the records would not be abused Any other conditions which individual depositors wish to impose would be respected by repositories, insofar as it would be practicable to do so

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[*] Copies of this memorandum can be obtained free from the Secretary, Records Preservation Section, British Records Association, The Charterhouse, London, E.C.1

[†] In the case of the files in which the clinical notes of each hospital patient are nowadays kept, it will almost certainly be necessary to resort to some process of sampling, a matter which is at present under careful consideration

The kind of record ‡ to be searched for will comprise

Foundation deeds, statutes and rules of medical societies and institutions, medical charities and dispensaries, and medical schools

Minute books of governing bodies and committees

Ledgers and main accounting records

Annual reports and balance sheets

Registers, such as those of students undergoing training or of patients admitted to hospital, where more than the patient's name is given

Letters written by medical men which may be of professional or personal interest, (the former may prescribe a course of treatment, give an opinion on a case or throw light on medical education, the latter may have biographical value)

Lecture notes, which may provide the only source of information for lectures of distinguished physicians and surgeons and give some indication of the state of knowledge of the time, and other students' notes

Licences (including letters testimonial) to practise medicine generally or in one of its branches

Partnership agreements

Account books and ledgers, which may contain information about the size of a doctor's practice, professional fees, the cost of drugs, &c

Case books and medical diaries

Prescription books

When the fate of any medical records is being considered, it would be wise to enlist the assistance of the Records Preservation Section of the British Records Association, county or borough archivists, the Royal College of Physicians of London, the Royal College of Surgeons of England, the Wellcome Historical Medical Library, or the National Register of Archives, with a view to arranging for their deposit in a suitable repository In order that medical and social historians, and others, may have ready access to this material, the Royal College of Physicians has agreed to act as a centre of information and advice on what should be kept or what may be found in the various repositories Copies of any lists of deposited records made by local archivists and reproduced by the National Register of Archives will be sent to the Royal College of Physicians, which will also pass on to the National Register of Archives information about the location of records which it receives These reports will, of course, be available to students at the central office of the National Register of Archives in Quality House off Chancery Lane, W C 2, on the same basis as other reports on various types of archives

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‡ Examples of many such records are given in the *Catalogue of an Exhibition of Medical Records* shown in 1958 at the Royal College of Physicians of London (published by the British Records Association, The Charterhouse, E C 1, price 2*s* 6*d*)

In England Now

A Running Commentary by Peripatetic Correspondents

THE other week we were discussing new research projects, and as one of our colleagues is interested in the medical aspects of boxing and another in head injuries, an experimental study of boxing pathology was suggested Of course this has been done already, but the older technique of creeping up behind some poor animal and hitting it on the head with a blunt instrument could surely be refined. Why not teach apes to box and have them knocked out under conditions of autonomic and endocrine discharge comparable to those of the ring? But someone pointed out that we might run into difficulties Boxing has been recommended by Professor Whitteridge as a sport eminently suitable for subhuman primates, but the Home Office is likely to disagree and might well refuse to allow such experiments on the grounds that boxing is too cruel a procedure to be used on the animals in relation to the new information likely to be gained And admittedly it could not be contended that the pathological findings would lead to new medical knowledge—that is, unless anyone has seriously suggested that blows to the head are beneficial to the brain.

* * *

For most husbands sleep is usually firmly on the credit side of the marriage balance-sheet Deep sleep at night, blissful dozing off in the companionship of an evening by the fireside, a brief nap after lunch until the washing-up is finished But for wives it seems to be different. Are men really the chief disturbers of the peace, or is it just that the women complain more?

" He sleeps nice enough until two in the morning Then he gets up and goes downstairs If that doesn't wake me, it's the pipes rattling as he fills the kettle at the sink So I lie there, listening to him moving around in the kitchen and wondering what he will be eating this time At three o'clock he's back in bed again and asleep at once, while with me, it's ages before I can get off His mother says his father used to be exactly the same "

" Seems at work he has a machine where he pushes something down with his foot and pulls down a lever with his hand So at night he has to start doing this in his sleep !"

" Well you know what his breathing's like, doctor, and on top of that, cough, cough best part of the night, and if that's not bad enough, he goes and covers his head with the blankets It's that queer and muffled like, I keep thinking he must be suffocating "

" He snores something really dreadful I had to move into our Pat's room with her, but we can still hear him through the wall "

" Well, I made a bad mistake I didn't know when I was well off Ted's all right, good fun to be out with, but he's jumpy, can't never keep still, even in bed Then he's sharp with the kids He smacked our Vera yesterday, right in the middle of Woolworth's, and she gave one scream out, 'I want my dad!' I could have sunk through the floor Now Nick was dead quiet, a twenty-four-hour-a-day sort of husband, and God help me, he let me sleep "

* * *

A faint reminiscent odour stole on my senses as I sat at the Comitia of the Royal College of Physicians Ripe apples, acetone bodies, there must be a diabetic close at hand, I reflected, and whispered my suspicion to the colleague on my right, hoping he was not the sufferer " Can't say I notice it myself," he replied—a heavy smoker perhaps—" But don't you think it might be the nail varnish of the lady on your left?"

* * *

" In winter time you will probably have to travel quite a lot by dog-sledge, and if you have skis bring them along " I left the Minister's office with a vision in my mind labelled " Doctor to the Great White North " Two weeks ago and well into the G W N I was introduced to my first dog-team The sledge seemed orthodox enough, but there were only three dogs—not the burly huskies of film and book, but a rather apologetic bunch Two were on their feet, one sat down and looked longingly at home I shouted " Mush " in an inquiring sort of way Surely every dog has heard of this word, but not my three Eventually by taking the lead at the traces I got them moving No 3 sat down for quite a while before getting up and trying to run back to the kennel Some yards further on I tired of running behind the sledge and hopped on to the runners The whole outfit stopped abruptly, and some mention was made f the shop steward—at least that is what it sounded like I limbed off, apologised, took the lead trace, and away we went gain. I soon took up my old position behind the sledge and it as two minutes before I noticed that the traces were slack ehind the dogs and that I was pushing the sledge across the e. I made a mental note that I had a lot to learn about driving dog-team and resolved to take skis the next time But it was n unhappy occasion. I shot off a snow-bank into the sea and nded my journey complete with skis and some incongruity in he back of a rowing boat. It seems that I have not yet settled he problem of transport.

* * *

I used to step smartly out of the front door on my eager ay to work Now I hesitate on the threshold, cautiously oke my head out, look both ways, and then proceed, only to hy again at the intersection of the garden paths You see, I ave acquired a new conditioned reflex. As an industrial nedical officer I have found that it is wise to assume that there s a "stacatruc" round every corner and a lorry at every rossing It is bad enough walking or driving across a network f railway lines, but at a steelworks you are liable to bump nto very hot pieces of metal as you try to avoid great ingots swinging through the air on unpredictable courses In coal-mines there is usually just time to flatten against the walls when unattended trucks come hurtling along rails that also serve as footpaths

I would like to put this explanation on record before it is assumed that the nerve of a once-intrepid hockey-player has finally gone On second thoughts, perhaps it has

* * *

Our Transatlantic friend is not accustomed to medicine in the Welfare State. Imagine her surprise when she attended the antenatal clinic of a London teaching hospital and Sister said "Can you spend a penny, dear?" As yet unfamiliar with the English idiom, she was only struck by the smallness of the sum "Sure I can spend a penny" she replied, "but what for?" Sister explained what was wanted "Oh! Urinalysis Gosh, that's cheap It would cost a dollar fifty back home!"

* * *

Overheard at the Club

" and he doesn't really know one end of a virus from the other "

* * *

BALLADE OF ACADEMIC *INEPTITUDE*

Well, no, I hadn't heard of that before,
(Doubtless it's common knowledge to the rest)
Written, you say, in 1834,
And published by a firm in Budapest?
I try not to admit that I'm impressed.
To me such virtuosity comes hard,
But to achieve it I shall do my best,
I write it down upon a little card.

Eager for knowledge, I read books galore,
Though reading tends to make me more depressed
Since each one read suggests a couple more,
Progression geometric spoils my quest.
In any case, I never could digest
So many facts, some I must disregard,
And others are more use if they're compressed.
I write it down upon a little card.

I never shall be a contributor
To learned journals, were I to suggest
A thesis, they would quietly deplore
Such rashness, though I meant it for the best.
It's very hard merely to keep abreast
Of modern trends I'm always on my guard
Lest I should miss something of interest,
I write it down upon a little card

Envoi

Prince, my despair shall not be manifest.
In spite of all I'll keep up the facade.
No-one shall know how much I am distressed,
I write it down upon a little card

Letters to the Editor

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—The report on bretylium tosylate by Professor McMichael and his colleagues in last week's *Lancet* will be of much interest to all concerned with the treatment of hypertension. As they point out, there has been great need of a drug which patients could tolerate with less difficulty than those which act by ganglion blockade Our experience has been of a similar group of patients treated over a similar period of time, and likewise many had previously been on pentolinium, mecamylamine, or pempidine In our hands, however, the results have been rather less promising, and the difficulties encountered force the conclusion that while bretylium is certainly an early probe into new territory, it has not been demonstrated over a sufficient period of time that it is a satisfactory drug for the routine treatment of hypertensive patients While there is no doubt that many of our patients previously treated with ganglion-blocking drugs have expressed pleasure at being relieved of the unpleasant side-effects which were the inevitable accompaniment of treatment, they have been unaware at this stage that their blood-pressures were still uncontrolled or only partially controlled When serial increases in dosage were necessary or new side-effects began to appear, fewer patients were heard to express satisfaction

We have found it best to begin with 100 mg ($^1/_2$ tablet) three times a day because some patients are very sensitive to the drug It usually takes several weeks or months to determine the optimal dosage

Difficulties in the control of blood-pressure with bretylium can be classified under three headings—tolerance, instability of the blood-pressure, and side-effects

(1) *Tolerance* —A preliminary fall in pressure has been recorded in most cases, but when kept under observation for several months a large proportion of patients (75%) have been found to require a steady increase in the dose in order to maintain control In several resistant cases control has been impossible Patients treated with bretylium must thus continue under the irksome close supervision which has been required to achieve satisfactory control with other drugs

It may be that combination of bretylium with a ganglion-blocking drug, each in relatively smaller dosage, and possibly also combined with chlorothiazide, will prove more effective, and our first attempts in this direction are fairly encouraging

(2) *Instability* —Fluctuations in blood-pressure have led to prolonged difficulty in stabilisation. We have observed considerable swings in pressure when recordings are made at hourly intervals through the day; so single readings in consulting-room or clinic may be very misleading Dizziness and occasional syncope have been alarming alike to patients and their medical attendants So far we have been lucky in avoiding disaster, but we are not surprised to learn that others have been less fortunate. The absorption studies reported from the Hammersmith Hospital provide a scientific basis for these clinical findings It may be that with increasing experience our technique of administration will improve, but low and variable absorption and relative lack of warning symptoms still constitute a major problem.

(3) *Side-effects* —It can be said at the outset that these have been less frequent and less severe than with any other effective drug used in the treatment of hypertension over the past ten years

Treatment has had to be abandoned on only two occasions, but, as can be seen from the following figures, the incidence of side-effects is high. Some are of considerable interest and merit discussion.

Side-effects in 40 Patients

Dizziness (not due to postural hypotension)	15	Nasal congestion	6
Chest constriction and paræsthesiæ	9	Headache	6
Parotid pain	9	Weakness	6
Diarrhœa	8	Salivation	3
Frequency	8	Sneezing	3
		Dyspnœa	3
		Tinnitus	3

Dizziness may, of course, be due to postural hypotension, but has also been a subjective complaint in many in whom the pressure is still high Since this symptom has not been a feature of treatment with other hypotensive drugs it must presumably be due to bretylium

A sense of *constriction or paræsthesiæ* across the chest and down the arms has been another unexplained complaint which in some ways simulates angina pectoris but bears no relation to effort and is not accompanied by electrocardiographic changes

Possibly both this symptom and dizziness are due to sensory disturbances in the distribution of the cervical and upper dorsal sympathetic nerves

Parotid pain may be severe and recur at the beginning of each meal or from sucking a sweet. It is not always associated with excessive salivation.

Diarrhœa is seldom troublesome, but in some patients it recurs with every increase in dose.

Frequency of micturition has been reported by patients of both sexes and is usually nocturnal Diarrhœa and frequency may perhaps be attributed to a swing from parasympathetic blockade to parasympathetic "release" and sympathetic blockade

Nasal stuffiness tends to persist but has not been disabling

Headache is presumably due to vasodilatation.

Weakness is an ill-defined sensation and we have no evidence that it is due to actual muscular paresis

There is some suggestive evidence that dyspnœa may be due to pulmonary œdema

In general, side-effects have been mild, and some of the ill-defined complaints may be due to autonomic imbalance, but further investigation is required for their elucidation.

We thought that a useful purpose might be served by grading our results in a similar manner to that described in the paper by Professor McMichael and his colleagues On this basis, as far as experience goes, we have obtained 50% of good results compared with their 60% We have been accustomed, however, to using somewhat different standards for grading results in that a good response has been claimed only if the standing diastolic pressure could be maintained at normal or near normal levels (and not simply a reduction of the diastolic pressure by, say, 20 mm Hg) By these criteria our proportion of satisfactory results with bretylium is lower

Experience to date would therefore seem to indicate, as the Hammersmith workers suggest, that bretylium, for all its advantages, is probably less reliable than the ganglion-blocking drugs at present available, but experience is still limited and it is too early to make a strict comparison.

From these observations it is clear that no highroad has opened before the hypertensive patient, and for this reason we feel strongly that a new compound such as this should not be widely recommended before the results of adequate clinical trials have been published, on a basis of which all clinicians can draw their own conclusions To do so is to invite difficulty, disappointment, and even disaster, since patients who are inadequately controlled may sustain severe postural hypotension and may even lose their lives from syncope, cerebrovascular accident, or myocardial infarction Without preliminary hospital assessment some will receive unnecessary treatment and others with serious hypertensive disease will receive inadequate treatment If patients living at a distance are discharged from hospital, it is far better that treatment should be continued under the supervision of a clinic or a physician thoroughly familiar with all aspects and difficulties of the treatment of hypertension, and where this is not possible it is better no to use relatively untried remedies

Those who intend to use such drugs should be aware of the difficulties, dangers, and possible side-effects, and these facts should be stressed in all recommendations fo treatment and in particular by the advertisers

We have no doubt that after 10 years of ganglion-blocking drugs a new era is beginning in the treatment of hypertension, and doubtless this is one of the first of a new series of very promising preparations Its chemical, pharmacological, hæmodynamic, and therapeutic effects are of very great interest and importance, and much credit is due to the research-workers responsible for its production, but it would be a profound mistake to imagine that the treatment of hypertension has been greatly simplified In a way it has become more complex, because now new possibilities exist and the relatively experienced physician may be tempted to dabble with mild cases or persist too long in resistant severe cases Before these drugs are widely used in practice far more experience should accumulate

Edinburgh

RICHARD TURNER
CLIFTON LOWTHER.

THE MARRIED MENTAL DEFECTIVE

SIR,—The follow-up study of married mental defectives in Sheffield, outlined by Dr Shaw and Dr Wright (Jan 30), is most interesting, but disturbing

Of the original 242 defectives, 45 are untraced, the majority of the remainder show an I Q distribution of between 50 and 69, a much higher birth-rate, infant-mortality rate, unemployment-rate, criminal record, and percentage of their children attending special schools than applies to the community at large

Live births were 50% greater than the norm for women married at the same age and for the same length of time, infant-mortality rates, such as are known, were very much greater than for the community at large (26 infants known to have died), a third of the families with one or more children were known to the National Society for the Prevention of Cruelty to Children or under the care of the children's department, and the percentage of their children at special schools seventeen times higher than for the Sheffield school population as a whole

Surely this *is* a clear-cut picture which demands some action other than the patience and forbearance and tolerance that the authors ask of other people in the same community? It is good to know that some of the defectives are leading normal lives Are the others offered birth-control advice, or indeed sterilisation . and, *if not*, why not?

The laws relating to sterilisation in this country are obscure, but most people agree that the subnormal couples with a large family and incapable of dealing with birth-control measures are eligible, if capable of giving consent, as also are those with subnormal mentality with a known eugenic chance of inheritance A high proportion of these families would seem to come into one or other of these categories Surely, if they are considered capable of making decisions to get married and have children, they must equally be capable of taking decisions about sterilisation?

Compulsory eugenic sterilisation is, of course, not legal, but I find it difficult to believe that some, at least, of such couples, faced with the difficulties that this survey brings to light, would be unwilling to accept birth-control advice or sterilisation, if offered it

London, N W 1

ELEANOR MEARS

PERTHES' DISEASE

SIR,—Your annotation last week on Perthes' disease is welcome, for it may call the attention of the medical profession beyond the restricted field of orthopædic surgeons towards this condition Nevertheless, it does not mention a factor which may be of decisive importance in its ætiology—namely, that with individual and very probably racial variations, from the age of three to eight years the blood-supply of the proximal femoral epiphysis comes through the small group of lateral epiphyseal vessels without complementary supply from the round ligament or the metaphyseal vessels This precarious system of blood-flow occurs, at least in the white child, until or before the age of eight years, while the children of African origin seem to preserve the fœtal circulation through the vessels of the ligamentum teres throughout childhood Perhaps for this reason the Negro child appears to be immune to Perthes', or at least seems to be only exceptionally affected by it as compared with the European child

As to the late consequences of Perthes' disease, in our analysis of over 125 cases we found that, as was to be expected, the only hips suffering from osteoarthritis in adulthood were those left by the early osteochondritis either misshaped or incongruent, or both Thus, to prevent this possible calamity all precautions should be taken, among them, for the moment, bed recumbency during the period when the dead bone is replaced by soft, malleable new cartilage

Nuffield Orthopædic Centre, Oxford J TRUETA

CONTROL OF ANTICOAGULANT THERAPY

SIR,—The isolated sentence from our paper quoted by Professor Quick (Jan. 30) was meant in no way to detract from the basic physiological and practical diagnostic merits of the one-stage prothrombin-time technique Still less could the sentence be construed as having any relevance to very different procedures like the thromboplastin generation test, the reasons for this cannot be given here, and no-one is more aware of them than Professor Quick. Indeed, the offending sentence has little meaning at all except within the context of anticoagulant therapy, which was the subject of our discussion

The acknowledged virtues of Professor Quick's test, described by us as a landmark in the physiology of coagulation, are too great to be seriously impugned by the recognition of certain limitations within a given context We specified and discussed the shortcomings we had in mind they refer only to the use of the unmodified test in the routine control of anticoagulant therapy and are not mentioned in Professor Quick's letter, while he appears to rebuke us for criticisms we did not make Surely he would not deny that unduly severe depression of true prothrombin and of factor IX can exist unrevealed by the one-stage test, and that bleeding does occur, though not often, when the clotting-time is within the therapeutic range With plasma from patients under coumarin treatment (though more doubtfully in the case of isolated deficiencies) thrombotest is sensitive to variations in all four factors concerned. Unlike the one-stage test it has been tailored to meet the requirements of anticoagulant control, successfully so far as we can judge though more extended trial should settle this question

One at least of Professor Quick's shafts—the glass-lined blood-vessels—was misfired, whether through misreading on his part or obscure writing on ours We did not list insensitivity to the contact factor as a shortcoming of the Quick test, but sensitivity to it as a disadvantage of thrombotest

Dr Laurie is quite right in his statement (Jan 23) of a much higher price for commercially supplied thrombotest reagent than the 4*d* per test suggested in our paper (Dec 26) This over-modest figure was innocently based on the value given for Customs purposes added to the duty charged—amounting in fact to 3½*d* per test We have since confirmed that the present cost per test of purchased reagent would be about 1*s* 6*d*, a price at which thrombotest, with all its technical virtues, would be unjustifiably dear for routine use in this country It is doubtful whether any test costing more than 6*d* for the reagent is worth while A way of reducing the cost of thrombotest may be found—e g, by using smaller volumes of blood and reagent, though so far our own experience with small volumes is not encouraging

Department of Pharmacology
and Therapeutics,
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Dundee

W WALKER
J M MATTHEWS

THE SIGN OF BABINSKI

SIR,—In your leading article last week, reviewing the history and significance of this sign—of which Walshe has written[1] that "there is perhaps no more important physical sign in clinical neurology"—you fail to mention the curious but surely relevant fact that the Babinski reflex can be demonstrated in many hypnotic subjects when regressed to infancy This is difficult to explain on the information available, unless there were some evidence of concurrent neurological or biochemical changes as a result of regression or the hypnotic trance itself But there is to date no such evidence

This phenomenon was investigated in America by Gidro-Frank and Buch,[2] who found that the change of response from plantar to extensor was accompanied by what they described as a reversal of the flexor-extensor chronaxie ratio, which, it was claimed, is normally the case in the truly infantile condition Later True and Stephenson [3] confirmed the presence of this reflex in subjects regressed to infancy, but showed that the E E G was nevertheless of the adult form. However, the genuineness of the phenomenon is still debated on both sides of the Atlantic and is, indeed, very difficult to prove, although most deep-trance hypnotic subjects will produce the response Gidro-Frank and Buch claimed that their subjects had no knowledge of the reflex or the intention of the investigators, but for my part I have not yet discovered a suitable subject of whom it could be said with certainty that there was no such knowledge But one subject, a student nurse in her first year, when deliberately misinformed and told with authority (as a temporary, experimental measure) that she had got it muddled and that the infantile response was flexor, nevertheless provided a first-class demonstration of the extensor reaction when regressed to the age of five months

Lower Beeding,
Horsham, Sussex

STEPHEN BLACK

SIR,—Your interesting editorial mentions instances of a temporary Babinski sign, rapidly reverting to normal A more gradual reversion can also occur in cerebral vascular disease

Examples of this were seen when 125 patients with hemiplegia, following cerebral vascular accident, were examined at fortnightly intervals for six months Some 53 of these cases showed an up-going toe on both sides the remaining 72 had a positive sign on one side only Out of these 178 responses, no less than 41 (25%) had returned to normal within six months Such reversion took less than two months in 8 patients, from two to four months in 14 patients, and more than four months in 17 patients 1 patient with bilateral Babinski signs showed reversion in one week on the left side and three months on the right side

Queen s Hospital,
Croydon.

TREVOR H HOWELL

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[1] Walshe F M R Diseases of the Nervous System Edinburgh 1940

[2] Gidro-Frank, L, Buch M K B *J nerv ment Dis* 1948, 107, 443

[3] True R M, Stephenson, C W *Personality*, 1951, 1, 252

CASE-FATALITY IN TEACHING AND NON-TEACHING HOSPITALS

SIR,—We should like to amplify the last paragraph of Mr Ellison Nash's letter of Jan 23

No doubt in the larger non-teaching hospitals all the night emergency anæsthetics are administered by junior staff, but this is not the case in many smaller hospitals Most provincial hospitals of 300-400 beds have establishment for only one resident anæsthetist—if they can find one On his nights off duty, usually six out of each fourteen, and for the first few months of each new appointment, every night anæsthetic is administered by a consultant.

In one such hospital of 300 beds, in 1958 the resident anæsthetist gave 342 anæsthetics for emergencies of all kinds, and the consultants, with 16 nominal sessions, gave or personally supervised 322 Some of these were when the consultants concerned were already in the hospital, considerably more than half entailed special visits outside their normal hospital hours

These figures are not exceptional, but probably represent the average for such hospitals

The quality of work must surely deteriorate under such conditions, where the individual is frequently tired before the start of a fresh routine day, whatever his actual status With advancing years recovery from a night's work is apt to be slower and less complete

Tunbridge Wells

ERIC FOWLER
RUSSELL M DAVIES

EFFECT OF BEER ON BLOOD FIBRINOLYTIC ACTIVITY

SIR,—Dr Ingram (Feb 6) cannot have read our paper very carefully We did not, as he suggests, compare the effect of a large volume (10-40 oz) of an alcoholic drink with that of a small volume (2 oz) on blood fibrinolytic activity It is stated both in the text and in the heading of table III that the 2 oz of whisky were taken in a pint of water A separate statement to this effect is not made about the results quoted in table I, and I think that it should have been, but this hardly justifies Dr Ingram's sweeping misquotation

Since he asks whether the lysis-time is prolonged by swallowing 10–40 oz of water, I can tell him from other experiments that it is not

Gloucestershire Royal Hospital,
Gloucester

G R FEARNLEY

AUTOTRANSFUSION IN RUPTURED ECTOPIC GESTATION

SIR,—Professor Chassar Moir in his letter of Jan 2 is the only contributor to the correspondence following Mr Azic's letter (Dec 12) who has mentioned the age of the blood from the peritoneal cavity, and he was not precise

Hamilton Bailey's *Emergency Surgery* counsels hesitation when the hæmorrhage is more than 10 hours old, and an earlier edition I believe gave 8 hours as a definite contraindication

In my experience in West Africa cases almost never presented as early as this, and in the several dozen cases I had to treat I never attempted autotransfusion In this course I was influenced by Hamilton Bailey, and by experience and teaching on first arrival abroad, because these cases did so well with immediate laparotomy alone, reviving almost dramatically from the time the bleeding point was clamped One gained the impression that if they had a pulse when they had been anæsthetised and reached the table, they would survive

I am not decrying the practice of transfusing freshly shed blood, but it seems an important point to know how late it may safely be used, for the guidance of those whose work lies in those areas where the average time before a ruptured ectopic is seen is probably well over 12 hours I have often wondered whether the use of blood too long shed has not contributed to an unsuccessful result, the advice to autotransfuse having been followed as long as the blood was fluid

London, N W 1

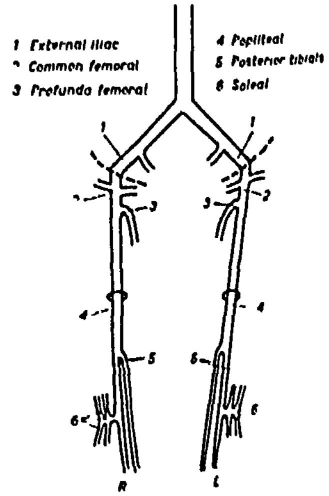
H DE GLANVILLE

ÆTIOLOGY AND PATHOGENESIS OF DEEP VEIN THROMBOSIS

SIR,—In his letter of Jan 16, Professor Quick states that *impaired circulation* is rarely, if ever, the primary cause of intravascular clotting and postulates that deep vein thrombosis is initiated by *local injury* of a vessel wall I take the opposite view, that a reduced venous flow is essential and that local injury is rarely the cause Of course, he states that the secondary added thrombosis is dependent on the locally formed thrombin not being swept away by a normal venous flow and thus slowing of the venous stream would explain propagation of thrombi

Local trauma cannot explain venous thrombosis in patients without injury (medical cases) or in those with injury away from the lower limbs, nor the multiple and varied distribution of the thrombi found at necropsy Routine dissection of the deep veins of the whole lower venous tree in patients dying after various injuries has shown that venous thrombosis is very common, that the frequency is related to advancing age and survival period (bed rest), that the nature of injury has little direct influence, and that a large variety of patterns of thrombosis occurs [1, 2]

These patterns indicate that thrombosis *begins* at one or more of several independent sites Six main primary sites are recognised (see accompanying figure) (1) the iliac vein, generally the external iliac vein just above the inguinal ligament, (2) the common femoral vein including the mouths of the medial and lateral circumflex veins, (3) the termination of the deep femoral vein, usually at a valve cusp guarding the ostium, (4) the popliteal vein near the adductor ring, (5) the posterior tibial vein, and (6) the intramuscular veins of the calf, particularly the soleal veins Thrombosis at one site is independent of thrombosis elsewhere and may then extend by forward propagation or retrogradely after occlusion of the lumen Only in this way can the various patterns of thrombosis found be explained



The frequency and extent of thrombosis are not related to the site of injury Thrombosis is common (50–80%) even in patients dying after injuries away from the lower limbs provided that they survive longer than 4–7 days and are older than 45–50 years Moreover, thrombosis is generally bilateral even in patients with injury confined to one limb

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1 Sevitt, S in Modern Trends in Accident Surgery and Medicine (edited by R Clarke, F G Badger, and S Sevitt), p 247 London, 1959
2 Sevitt S, Gallagher, N G (in the press)

The multiplicity of primary foci and the lack of relationship of thrombosis to the site or side of injury cannot be explained by local trauma, and this is supported by histological observations which show that recent thrombi are laid down on normal endothelium

That advancing age and duration of bed rest (survival period) are the most important factors predisposing to thrombosis supports the old contention that venous stasis plays a major ætiological role. This is also supported by abundant evidence that the blood-flow through the lower limbs is greatly slowed during bed rest

Emptying of veins depends on muscle contraction, and lack of this, particularly in the elderly put to bed for any reason, will allow the blood in the lower limbs to become stagnant Thus, anatomy and the dynamics of blood-flow decide where thrombi *begin* to form. Thrombosis occurs in the soleal veins because they become distended with stagnant blood in the horizontal position of bed rest and, as shown by Gibbs[3], because they form a number of inverted intramuscular arcades which increase in number and lumen diameter with advancing age Thrombosis of the posterior tibial veins is possibly encouraged by the relationship of the vein to the upper edge of the soleus muscle, whilst the deep intramuscular location of the profunda femoris vein and pressure from the overlying adductor muscles help to slow its venous stream. Further, the inguinal ligament facilitates thrombosis in the common femoral vein because it may compress the vein when the thigh is flexed on the trunk, as in Fowler's position. Eddying of the stagnant blood-flow with consequent local silting of platelets and leucocytes on to endothelium probably plays a part in initiating thrombosis at least in the thigh and pelvic veins Eddying and silting is likely to occur at valves and mouths of vein junctions at the termination of the profunda femoris, medial and lateral circumflex veins, and other tributaries of the common femoral vein Above the inguinal ligament eddying and silting may initiate thrombosis in the external iliac vein because, when the body is horizontal, there is an acute weir-like change in direction of the slowed column of blood In short, the common denominator of venous thrombosis is venous stasis, and, in addition to venous anatomy, which determines eddying, silting, and primary location of thrombi, the major roles are played by age, immobility, and above all bed rest. Injury per se rarely, if ever, plays an ætiological role

Birmingham Accident Hospital S SEVITT

BREECH PRESENTATION AND DELIVERY

SIR,—It would be a pity if external version were not to be attempted The breech presentation is uncomfortable for the patient, and rightly or wrongly the expectant mother is nearly always apprehensive about it Before anyone attempts version, however, he or she must clearly understand that there are two kinds of breech, " a cylinder within a cylinder, and a sphere within a sphere " The former will not turn and can only very rarely be turned, the latter will probably turn themselves (but not certainly) They can, however, be turned, so why not? Vigorous attempts to turn the first type in the antenatal clinic are to be condemned and attempts under anæsthesia should certainly be abolished Anyone who has had a disaster with version and has proved himself "accident-prone" should give it up

The only exceptions I make are (1) if a woman is to be induced under anæsthesia then I would try a version first, (2) occasionally conditions are encountered which would be suitable if the patient could cooperate, but she won't

What is much more serious is the steadily increasing cæsarean-section rate in one hospital over half of the breeches were section in one year By surgical induction the size of the baby can be controlled In this way dystocia will be avoided, and we must all admit that dystocia in the breech is more troublesome than in the cephalic presentation By a wider use of surgical induction, the rate of cæsarean section with all its potential dangers can be kept within responsible limits

London, W 1 C K. VARTAN

THE ABNORMAL APPENDIX

SIR,—May I criticise Mr Jewers' reasons (Dec 26) for preferring a paramedian incision?

Firstly I disagree about the ease of approaching the appendix, especially the retrocæcal variety in most cases the appendix can be removed easily through a gridiron incision. If the skin incision is made obliquely transverse in a natural skin crease following Langer's lines the incision can readily be extended laterally or medially In dealing with a retrocæcal appendix, which more often lies towards the outer side of the ascending colon, I make my incision rather higher than usual and of adequate length, and have rarely found it necessary to use retractors, provided a good anæsthetic is given, which is most important. On the other hand, removing a similarly positioned appendix via a paramedian incision has always appeared difficult to me Even when the tip of the appendix is lying towards the midline the base may still be found well out in the right iliac fossa and appendicectomy is still carried out more easily by the more direct approach of a gridiron incision

Secondly, I consider the routine use of a paramedian incision, in case one's diagnosis is wrong, is to be deprecated, as it must encourage an attitude of mind whereby any case of abdominal pain is subjected to an exploratory laparotomy I know it is often said that it is far better to take out a normal appendix than to miss a pathological one, but I have a feeling that too many patients are subjected to a laparotomy for abdominal pain and a normal appendix removed to justify this procedure Even though the risk to life is minimal, it is never non-existent, and in addition to the risk of an anæsthetic death, there is that of intestinal obstruction at a later date from adhesions, and this is greater after a paramedian incision than after a gridiron.

It is preferable to observe the patient for a time if the indication for operation is not clear rather than submit a person to a rushed operation, for it will often be found to be unnecessary In a series of 324 patients admitted to hospital as emergencies with abdominal pain and mostly seen by me, operation was performed for acute appendicitis in 158, conservative treatment for acute appendicitis was instituted in 21, and 59 cases of abdominal pain in which no accurate diagnosis was made initially were observed In many of this last group no final diagnosis was reached There were no deaths in any of these groups Thus, a fairly high proportion of patients admitted as acute abdominal emergencies are found to have very little wrong with them, this applying particularly to the younger female group

Conversely, as Mr Jewers has pointed out, the symptoms and signs in the elderly are singularly lacking, but early diagnosis and operation is as imperative as in the very young I have operated on a number of people over 75, including a few in the 80s, and have found that localisation of the infection is remarkably poor, especially in the obese Severe peritonitis may be present with a normal pulse and temperature and only minimal signs in the abdomen, but invariably there is localised tenderness, however slight, over the appendix In fact, I would go so far as to say that in any case of suspected acute appendicitis unless this tenderness is present I would question the diagnosis Occasionally, of course, one is sure of some intra-abdominal mischief, but the exact diagnosis is obscure, and in these cases I quite agree with the use of a paramedian incision, but as a rule the commonest conditions with which acute appendicitis may be confused lie in the lower abdomen, and these can be dealt with efficiently by extending the gridiron incision medially and dividing the right rectus muscle transversely The wound heals quickly and soundly

Lastly, citing a low incidence of hernia after a paramedian

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3 Gibbs, N M *Brit J Surg* 1951, 45, 209

incision as an argument for adopting this approach is surely contrary to general opinion An incisional hernia after such an incision is not infrequent, whereas I have seen a similar hernia after a gridiron incision once only Regrettably, this was one of my own cases, but the patient was obese, and developed a severe wound infection Fortunately, the repair of this was easy But perhaps the fact that there is a greater incidence of right inguinal hernia in those having had an appendicectomy is what is implied

Let me say that I found much of Mr Jewers' paper excellent—and in particular the remarks on the use of antibiotics were most relevant Too often a course of these drugs is started immediately appendicitis comes to mind, even when the infection is mild or non-existent In the late case treated conservatively a long course of antibiotics is not without danger

I remember well a man who had been ill for three weeks before admission being given prolonged chemotherapy, and at operation several months later I removed his appendix and drained a chronic encysted pelvic abscess Postoperative obstruction developed, requiring further operation, from which he subsequently died

My findings regarding the position of the appendix also confirm what Mr Jewers says The figure usually quoted of 0 5% [1,2] for the retro-ileal position has always seemed too low, while that of 21% [2] or 32% [1] for the pelvic appendix too high Although I have not exact figures available, I have the impression that in my experience the retro-ileal occurs in 5% of cases at least Probably the percentage of pelvic appendices mentioned is elevated by including many cases of subcæcal ones I would not class an appendix as of the pelvic variety unless a part of it is definitely hanging over the pelvic brim On the other hand, I would consider the high retrocæcal appendix due to a maldescended cæcum comparatively rare, whereas that with the cæcum in a relatively normal position is common, the tip of the appendix being found at varying heights behind the ascending colon to as far as the hepatic flexure These usually require removal by the retrograde method, since they are buried in the retrocolic tissues

Grove Park Hospital,
London, S E 12

R F BOLAM

TREATMENT OF INFECTIONS IN HOSPITAL

SIR,—Your annotation of Jan 16 discussed the report of Finland et al on the changing pattern of infections Once again the seriousness of staphylococcal infections was demonstrated

That the old enemy, the hæmolytic streptococcus, is not yet beaten has been suggested by the rather disturbing increase in the isolation of this organism from the throats of children in this area Not only has there been an epidemic of β-hæmolytic streptococcal throat infection in a large school, but also this organism has been isolated from more than a quarter of the throat swabs taken in one children's ward during the past year

During the same period, the number of cases of acute rheumatism and acute glomerulonephritis seemed to be on the increase, so an analysis of the number of medical (as opposed to surgical) patients admitted to three children's wards during the past five years has been made Practically all sick children from this part of the Black Country are admitted to one of these three units All were fresh cases, and subsequent admissions for the same disease have been excluded

Year	*Total admissions*	*Acute rheumatism*	*Acute nephritis*
1955	945	8 (*0 85%*)	11 (*1 16%*)
1956	1014	14 (*1 38%*)	12 (*1 18%*)
1957	1054	5 (*0 47%*)	11 (*1 04%*)
1958	1095	6 (*0 55%*)	6 (*0 55%*)
1959	1169	38 (*3 26%*)	20 (*1 7%*)

From these figures it will be seen that there has been a striking increase in the admission of patients with acute rheumatism and a definite, but less remarkable, rise in the number of children suffering from acute glomerulonephritis One wonders whether this increase in the number of streptococcal infections is widespread If so, is it because penicillin is less frequently used for throat infections at the present time? The broad-spectrum antibiotics which are so often prescribed at present are known to be less effective than penicillin against the streptococcus Or can the commonly occurring penicillin-resistant *Staphylococcus aureus*, concomitantly present, produce enough penicillinase to render the streptococcus less sensitive to penicillin?

Wolverhampton

H EVERLEY JONES

THE COST OF DRUG TREATMENT

SIR,—Recent letters on this subject have made me break a resolution formed some time ago not to send another communication to the Press My present breach is in spite of a conviction that any letter on the subject is only " a voice crying in the wilderness ", but this letter is chiefly to endorse Sir Max Page's remark (Jan 30) that " Savings on drug expenditure leave more money for hospital building, more doctors and more pay for them "

The subject has interested me more particularly since, as adviser on venereal diseases to the Ministry of Health, when, in 1920, I wanted to find money not then available for improvements in the V D service, I began to examine in detail the expenditure of the clinics, hoping that by checking waste the money already being expended could be used to better purpose My investigation revealed waste, sometimes of the most idiotic kind, and prompted economies, *by persuasion*, that resulted in very substantial saving in the cost of the service The experience during the decade 1920–30 convinced me that the average doctor does not give a thought to the question " is this drug in this form and this amount necessary? "

I described the methods by which economies were effected first in 1923 in an article entitled Economy in Drugs and Dressings, which was contributed, by invitation of Dr F N K (later Sir Frederick) Menzies, to the 5th annual report of the Order of St John and the British Red Cross Society on the Voluntary Hospitals in Great Britain, and next in 1951 in a letter to *The Spectator* (Jan 19, p 79) to support an article by Dr M E Lampard, published a fortnight previously in the same periodical, under the title Doctors and Drugs, in which he exclaimed at the waste that was then prevalent I ended that letter with the following remarks " If anyone reading Dr Lampard's article and this letter is tempted to embark on economies in his branch of the N H S, he should not expect thanks I should like to meet anyone who has been thanked for saving public money "

I learnt the importance of economy in drugs quite early in life, being a son of a practitioner who dispensed his own prescriptions Later, as assistant to a country practitioner, I put my knowledge to some use in frequent gentle reproofs of my boss for the cost of his mixtures Still later, in India, when one of my duties was charge of a cantonment hospital, for native civilians, I had to work to a budget which did not err on the side of extravagance and I had to find the money for new instruments, such as cataract knives, by watching every anna It was a very useful experience and it prompts me to suggest that if doctors had to work to budgets in respect of drugs, dressings, and instruments—budgets *framed by people with practical experience*—we should see the taxpayers' money used to better purpose in that branch than at present I know because I have tried it and it has worked Often in my visits to V D clinics I was asked by a medical officer if he could have such and such a rather expensive instrument or apparatus, and from information as to the details of his expenditure in his clinic, read in the light of my experience in my own clinic, I was able to tell him how to save enough to buy the tool he wanted

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[1] Aird, I A Companion in Surgical Studies, p 856 Edinburgh, 1957
[2] Bailey, H, Love, M A Short Practice of Surgery, p 587 London, 1959

London, S W 1 L W **HARRISON**

SIR,—Dr Miller and Dr Smith (Jan 2) make the retail pharmacist the scapegoat for the rising drug bill As a retail pharmacist and one-time hospital chief pharmacist, may I reply to the criticism of excessive distributive costs which suggests that retail pharmacists are overpaid for their services

The argument rests on the disparity between the basic cost of drugs and the final cost which is determined by the profit or fee paid to the pharmacist. There is, however, no logical connection between the basic cost and fees paid for distribution Phenobarbitone is cheap, but why should the pharmacist's fee be related to the cost of phenobarbitone? The cost of the general medical practitioner's share in the distribution of phenobarbitone is at least equal to that of the pharmacist, but no-one would suggest that medical fees should be assessed in this way The pharmacist's fee is related to the cost of providing centres for distribution of drugs as well as for the actual dispensing services In relation to the actual costs of providing the service, the pharmacist is not overpaid—even if the cost of distribution is one-third of the drug bill Not many pharmacists earn more than £1000 per annum from dispensing

The comparison with hospital costs is most misleading—it is very difficult in hospital costing to relate costs to any unit of work. The hospital pharmacist makes many economies for the management committee by judicious buying, but comparative costs would have to include a proportion of maintenance that your contributors ignore.

It is not generally recognised what a good service the patient gets from the retail pharmacist, who daily has to obtain quickly new proprietaries and who cannot substitute chemical "equivalents" as is done in the hospitals It is, of course, quite true that a more rational distribution of drugs and of medical services could be devised, but costs would still have to be related to many other factors apart from basic prices of drugs

London, E C 1 W C **KING**

SKIN CHANGES IN HYPOCALCÆMIA

SIR,—The paper by Professor Dent and Dr Garretts (Jan 16) leads me to record a further case confirming their findings, but I also wish to point out that the presenting feature in this patient was his mental state

A 64-year-old man was recently admitted to hospital suffering from quite severe depression, retardation, and lack of initiative He had widespread scaling of the skin, especially on the arms There was bluish-red erythema in the folds of the groins with some oozing He had generalised muscular hypotonia and passed bulky stools The following tests were carried out

Blood-picture showed anæmia with some macrocytosis

Glucose-tolerance test showed sugar levels of 86, 81, 111, 113, and 106 mg per 100 ml at half-hourly intervals No glycosuria

Serum-protein 6 1 g (albumin 3 8 g, globulin 2 3 g) per 100 ml Serum-calcium 6 7 mg, phosphorus 3 0 mg, bilirubin (direct negative) 0 5 mg, thymol turbidity 2 units, zinc turbidity 5 units, alkaline-phosphatase 30 King-Armstrong units per 100 ml

Faeces 72-hours total fat 108 g (80% total solids), split fat 93 g (68% total fat)

Almost certainly a case of idiopathic steatorrhœa, he is being treated, with improvement, by folic acid, 'Parentrovite', and imipramine.

The skin lesions have been recurrent for sixteen years His psychiatric history reveals that he had electroconvulsion therapy for depression in two other hospitals in 1952 and 1954 He was a patient here in 1955 and last year, on both occasions in a state of hypomania In 1955 his serum-calcium was 9 5 mg per 100 ml, and there was only slight scaling of the arms

Thus his "skin health" seems associated with his blood-calcium level An episode of depression accompanied the hypocalcæmia, and as 2 of Professor Dent and Dr Garretts' 4 cases showed states of acute anxiety and suicide-level depression, I think it is essential to emphasise the dangers, from a psychiatric point of view, in this condition

I wish to thank Dr J A S Mulligan for permission to publish this case

St. Luke's Hospital,
Armagh W A. **GORDON MACCALLUM**

SIR,—We are interested to note the point raised last week by Dr Brian Russell, whose patient with erythrodermia did not show a correlation between the rash and the hypocalcæmia We are not surprised about this as we intended to state in our paper that it is only in certain patients that such a correlation can be noted The vast majority of patients with hypocalcæmia do not get any sort of skin trouble, and the majority with various forms of skin trouble do not have hypocalcæmia The point of our paper was only to state that sometimes there was such a correlation between hypocalcæmia and skin disease and that in such cases it was important to deal with it as there was no other treatment We are sorry if it was not clear enough in our paper

University College Hospital Medical
School, London, W C 1

C E **DENT**
M **GARRETTS**

INFANTILE STRUCTURAL SCOLIOSIS

SIR,—Your annotation of Jan. 30 is a curious one It says "there is much to be gained by the further study of the natural history of severe deformities, and until this is understood it is wrong to claim that any particular treatment has been successful" I would find this easier to understand if I knew what methods and what claims were being referred to I do not appear in the list of references, but as far as I know I am the only surgeon to suggest[1] that the terrible deformity of "idiopathic scoliosis" starts in utero, and can be detected in early infancy and cured at that stage by splinting and physiotherapy The present teaching of orthopædic surgeons appears to be that because some cases get better spontaneously therefore none at all should be treated

I do not know what they would reply to the mother of a child with "severe and progressive scoliosis" who says, as several have said to me, "I kept telling them that the baby's spine was crooked, and they just laughed at me"

I have aroused considerable resentment by suggesting that treatment is absent because there is no classical splint to reverse the curve of the spine, any more than there is one to reverse the commonest of all elements in deformities of the feet—that of equinus

London, W 1 **DENIS BROWNE**

*** The prime object of our leaders and annotations is to note and discuss new work we hardly ever aim at a comprehensive review and an exhaustive list of references In this annotation we were concerned with the recently published work of James et al and not with all the possible ætiological factors that might combine to produce the condition We thus excuse ourselves for feeling no need to recall Mr Denis Browne's considerable and well-known contributions to this subject We still affirm that the best treatment is usually based on a knowledge of what causes natural resolution It was never our intention to suggest that *no* deformities should be treated —ED L

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[1] Browne, D *Proc R Soc Med* 1956, 49, 395

ANTI-SMOKING CAMPAIGN

SIR,—The article last week on the efficacy of an anti-smoking campaign is full of interest It is not surprising that it failed to diminish the amount of smoking, because " drug addicts " cannot be cured by exhortation, the only remedy is to make a harmless cigarette that people will smoke

It is interesting that after the campaign there was evidence that people realised to a greater extent the harm done to bronchitic people, but it did *not* increase the awareness of the connection between smoking and cancer of the lung The authors are undoubtedly correct in saying that this is a form of " emotional blockage " due to fear of cancer " long nurtured by a conspiracy of silence " This psychological problem can best be solved by personal conversations between a lay person and a member of the nursing profession—i e, health visitors, district nurses, and midwives If local authorities would spend half the time, money, and energy at present spent on anti-smoking campaigns in arranging for their nurses to talk to the public about the symptoms of the " accessible cancers " they would get immediate results

Oxford MALCOLM DONALDSON

CASUALTIES AND CASUALS

SIR,—Two points may influence Dr Fry's conclusions (Jan 16) and Dr Doyne Bell's comments upon them (Jan 30)

Both doctors are Londoners London has a large " floating population " which increases the number of " casuals "—travellers, troupers, workmen on location, and so on They have no family doctor near them because they have no family life They have a right, one might think, to look to the nearest hospital when they are in need All casualty departments have a few of these patients, but London has a lot

Secondly, the little clinics doing family doctor's work which have developed in casualty departments grow by what they feed on The more they are treated, the more they come Dr Fry seems to disapprove of them, and so do I Nevertheless, if I remember rightly many young casualty officers did not discourage these opportunities to try their wings, from the shelter of their hospitals, before launching out upon more serious flights If the hospitals themselves disapprove nowadays, I do not think they did so always

My first point is that this work should not entirely disappear, and my second that to a very large extent the volume of it depends upon what you make it A consistent policy about what one's own casualty department considers it should treat, and what can be treated equally well or better in the doctor's surgery, can of itself determine in which way the work develops I have misgivings about national decisions about what casualty departments as a whole should or should not do

Dr Doyne Bell refers to the " consultant who is ultimately responsible " and to the difficulty of deciding which particular specialist would be the most appropriate I often wonder what this ultimate responsibility means, and suspect its interpretation in many minds would be " carrying the can " Strict conformity with the limits each specialty sets for itself could reduce casualty department work to a farce, and I detect signs that the farce is likely to begin before long The casualty department cuts across all specialties Because it is very often concerned in emergencies and accidents *of all types* it would be a grea mistake for it to be gathered into any particular sphere of specialist influence In most hospitals, on the other hand, staffing problems make it impossible to share the work amongst all the different specialties concerned The sooner we accept that the casualty department is *part of the hospital* as a whole, and that it should command the support of all the faculties, the better for the hospital service

As a surgeon, I should like to agree with Dr Doyne Bell that our casualty departments could be defined as accident, emergency, and dressing stations I do agree that we could make many of them much more like his definition than they are *As a doctor, I see* quite a number of cases outside his definition that I *simply* cannot send away

Sunderland T G LOWDEN

NATURAL HISTORY OF CAVERNOUS HAEMANGIOMATA

SIR,—

" In Xanadu did Kubla Khan
A stately pleasure dome decree
Where Alph, the sacred river, ran
Through caverns measureless to man
Down to a sunless sea "

According to the correspondence in your columns cavernous hæmangiomata appear to be measureless to man's judgment, but I believe the main body of opinion in the many letters gives the truth of the matter So I would have left it, but I have been invoked as an authority and I am convinced that spontaneous resolution, usually in the first decade, is the rule, and I can recall seeing only three adults with lesions of this type However, the obvious lesions, especially those on the face, cause much distress to the parents, and it is usually possible to hasten natural resolution by X-ray dosage well within the safety margin

When parents wish for something to be done I prefer to use X-rays with a half-layer value of 1 mm., or not exceeding 1 5 mm., of aluminium with a dosage of 250r, repeated after a month's interval for three doses Smaller lesions can sometimes be given 300r, and exceptionally four doses might be given. Within this range no erythematous reactions were observed nor any atrophic sequelæ No irradiation was given in the vicinity of the thyroid glands For many years treatment was not given to lesions which were hidden by clothing, and those all disappeared satisfactorily well within the first decade

London, W 1 REGINALD T BRAIN

SIR,—I read Dr Simpson's excellent article (Dec 12) with great interest and I am in full agreement with all the supporters of the " wait and watch " school My only excuse for this letter is to quote from the writings of an acute clinical observer of the pre-X-ray and pre-carbon-dioxide-snow era—Thomas Bateman *In the 6th edition* of his book, *A Practical Synopsis of Cutaneous Diseases*, according to the arrangement of Dr Willan, published in 1824, on p 331 he writes of this group of nævi

> " Some of these excrescences are raised upon a neck or pedicle, while some are sessile upon a broad base Some of *them again*, although vivid for some time after birth, gradually fade and disappear some remain stationary through life, but commonly vary in intensity of colour at different seasons and under circumstances easily explained and others begin to grow and extend, sometimes immediately after birth, and sometimes from incidental causes at a subsequent period, and from small beginnings become large and formidable bloody tumours, readily bursting, and pouring out impetuous and alarming hæmorrhages, which, if they do not prove suddenly fatal, materially injure the health by the frequent depletion of the system Sometimes, however, after having increased to a certain degree, they cease to enlarge, and thenceforth continue stationary, or gradually diminish, till scarcely any vestige remains '

There is no doubt from this that Bateman was aware of the spontaneous resolution of these lesions The graphic description of "impetuous and alarming hæmorrhages" tells of a course of events which nowadays must be extremely uncommon but may possibly account for the surgical emergencies of which Mr Denis Browne writes

I, along with many other dermatologists, would welcome the opportunity of seeing some of the adult patients with cavernous hæmangiomata whom Dr Colin-Jones (Jan 2) meets so frequently in Sussex As Mr McLaughlin states (Jan 16), to treat or not to treat is still one of the most difficult questions in dealing with cosmetic problems

Oxford. H R. VICKERS

INTRATHECAL PHENOL IN THE TREATMENT OF SPASTICITY

SIR,—I wonder whether an interested reader who has treated no patients by this technique and who has made no contribution to the subject can add a comment to the recent correspondence regarding the history of this method of treatment

Dr Maher's original work on the use of this technique in the treatment of pain, particularly in malignant conditions, is acknowledged by the writers concerned So far, however, I have seen no reference to the fact that in the second of his papers (January 1957)[1] there is a brief but favourable mention of his use of this treatment in a case of hemiplegia with severe flexor spasms This was, I believe, the case referred to by Dr Liversedge in his letter of Jan 2 in which improvement has been maintained over a period of three-and-a-half years

I am drawing attention to this reference in the interest of accuracy

Oldham J STARKIE

DIAGNOSIS OF MULTIPLE PREGNANCIES

SIR,—In your annotation of Jan 30 you make the remarkable claim that multiple pregnancy can be demonstrated by the electroencephalogram The annotation would have little value did it not imply the maternal electroencephalogram!

It is, of course, well known that sensitive balanced recording amplifiers of the type used in electroencephalographs, when connected to electrodes placed on the abdomen of a pregnant patient, will record the R waves of the fœtal heart or hearts[2] This technique is in general use in many obstetric hospitals and over 200 papers have been published on the subject in the past 40 years

The time constants of the electroencephalograph type of amplifier are not ideal for the purpose and a greater degree of success can be achieved by following the design recommendations of Bell.[3] The maximum energy in the fœtal R wave occurs in about 0 02 second. An amplifier with a time constant of 0 02 second and restricted band-width will give success in almost every case. As you mention, around the 30th week of gestation recording is difficult, this is due to excess vernix caseosa

Recent work[4] has shown that the presence of a fœtal QRS complex is not always a sign of life, for it may sometimes be obtained from a severely macerated fœtus

In the diagnosis of multiple pregnancy it should be remembered that fœtal electrocardiography may indicate single pregnancy if one of twins is stillborn.

An advantage of using an E.E.G machine for fœtal cardiography is that it will also read the electroencephalogram from the maternal abdominal surface and on occasions show slow waves of large amplitude Such waves are characteristic of gross anoxia in the newborn and may indicate the same condition in the fœtus also

University College Obstetric Hospital,
London, W C 1 C. N SMYTH

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[1] Lancet 1957, i, 16

[2] Smyth C N Lancet, 1953, i 1124

[3] Bell G H J Obstet Gynæc Brit Emp 1938 45, 602

[4] Smyth, C N , Farrow, J L Brit med J 1958, ii, 1005

HYPOTHERMIA FOR NEUROSURGERY DURING PREGNANCY

SIR,—The report[1] on hypothermia and hypotension in a pregnant woman was of particular interest to me

On March 31, 1958, eight months prior to the admission of Wilson and Sedzimir's patient, a woman aged 34 years, who was twenty-four weeks pregnant, was sent to the neurosurgical unit of St. George's Hospital (Atkinson Morley's Hospital) after a cerebrovascular accident.

Examination revealed a normal fœtal heart, and neurological investigation showed that the patient had bled from a right parietal angioma.

The position and size of the tumour was such that it was decided to operate under hypothermia and in the sitting position (bolt upright)—as if for a posterior-fossa tumour Mr Wylie McKissock completely excised the tumour and the patient made an uneventful and successful recovery

Following induction of hypothermia the fœtal heart-rate fell from a preoperative 180 to 120 per min. at 30°C, but always remained regular and returned to normal after the mother's body temperature had been restored.

The pregnancy came to full term and the child was delivered normally with the full cooperation of the mother Both mother and child are doing well.

This case is to form part of a paper on a simplified technique for large-scale hypothermia for neurosurgery

Cape Town. JACK LEVIN

PREVENTION AND TREATMENT OF BEDSORES

SIR,—Dr Roberts (Jan 30) has drawn attention to a subject which deserves a very full study 33 out of 250 patients (13 2%) treated in a geriatric unit during the past four months were found to have bedsores at the time of their admission The stay in hospital of such patients is often prolonged (on average, it was 40 days as against 25½ days for those without bedsores) Moreover, the mortality is four times as great if pressure sores are present The study of factors leading to the development of bedsores is therefore an important aspect of preventive medicine, and the interest of medical officers of health and district nurses in this matter is to be welcomed

It is generally recognised that all patients who are nursed in bed—and especially the elderly—are exposed to the danger of pressure sores The risk, however, varies considerably with different types of patient, and it is greatest for those whose general condition is poor Because of this variation in risk the comparison of the value of different prophylactic procedures is difficult. In order that an assessment can be made more accurately we have been using a scoring system based on the patient's physical condition, his mental state, his activity, his ability to change position in bed unaided, and the degree of incontinence when this exists The scoring can be carried out simply, and closely similar results are obtained by different observers With this system possible scores are within the range of 5–20, and by making the score on admission to hospital and at weekly intervals the change in the patient's condition during the course of his illness can be assessed The average score for patients who already had pressure sores was 11 0 on admission, and of those who developed pressure sores in hospital it was 12 3 initially and 11 1 at the time the sore developed Those patients without pressure sores had an average score of 15 4

Our preliminary observations indicate the fundamental importance of the general condition of the patient in determining the likelihood of development of pressure sores We believe that this study will also allow a comparison to be made of the effectiveness of different nursing procedures in groups of patients with a variety of diseases While it is possible that many of the traditional procedures, such as the application of spirit and powder and the rubbing in of soap, have little to commend them, the evidence so far submitted in favour of silicone creams is not conclusive At the moment the widespread use of these expensive creams as a prophylactic measure for all patients who are nursed in bed either at home or in hospital is in our opinion unjustified Large trials conducted by local health authorities and by medical and nursing teams in hospital are urgently required

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[1] Wilson, F , Sedzimir, C B Lancet, 1959, ii, 947

Whittington Hospital,
Highgate Wing, London, N 19

A N EXTON-SMITH
DOREEN NORTON

DIAGNOSIS OF BRUCELLOSIS

SIR,—Your review (Jan 30) of my book agrees with me that we know little about this disease It was for that reason that I wrote the book on brucellosis in England I have evidently failed in my task, for your conclusion is that "many physicians will be unconvinced by the diagnosis in at least half the patients" The only reason you give for this extraordinary statement is that a rise in the titre of agglutinins after an injection of brucellin can be demonstrated in some apparently normal subjects

I took as my criteria of diagnosis those advised by Wilson and Miles in a standard textbook [1] of bacteriology and immunology In not one of my cases was "therapeutic success" used as the diagnostic weapon you suggest Every one was confirmed by either an initial agglutination titre of 1 in 80, or a positive skin test, or a fourfold rise in agglutination titre after the skin test if that was negative

Aside from this backing by eminent authorities I feel that your argument is a weak one You might as well say that because many apparently normal persons have a positive reaction to the Mantoux test you do not believe that they have ever been infected with the tubercle bacillus "Apparently normal" people may have a positive serum reaction for syphilis, toxoplasmosis, or other disease Are we therefore to abandon the use of these tests and to ignore their results? It is true that the clinical history is important in the diagnosis of brucellosis, and indeed it is often the crucial factor in deciding whether to treat or not Wilson and Miles say "The interpretation of the agglutination test is not always easy, and demands a knowledge of the clinical history and the occupation of the patient" They also give this criterion which is less stringent than mine "A titre of 1 in 20 to 1 in 80, in the presence of clinically undulant fever, may likewise be considered as practically diagnostic of this disease"

You are also guilty of a misuse of words You say that my conclusions are dogmatic Dogmatic means based on a-priori assumptions which are incapable of proof If you read the book again carefully you will see that all the conclusions were based on the work of other investigators or my own observations They cannot therefore be called dogmatic Everyone who has anything original or unusual to put forward must expect to be disbelieved I know that the correct thing to do with an ill-informed review is to ignore it, but it is important for the sake of the patients to protest in this case So long as this unfortunate attitude of *disbelief* is exhibited towards the manifestations of chronic brucellosis, so long will cases be missed and much suffering which could be prevented will continue

Bath HUGH WALLIS

⁂ Of Dr Wallis' 35 proven cases, we make it that 15 were diagnosed by agglutination tests, 2 by skin tests alone, and 18 by a fourfold rise in agglutination titres *after* the injection of brucellin

We accept the evidence of the agglutination tests, with the proviso that no single test confirms a diagnosis beyond any possible doubt.

Of the skin test, Wilson and Miles (p 1911) say

> "Generally speaking the reaction resembles the tuberculin reaction in denoting the occurrence of infection without giving any clear indication of its activity , it may then remain positive for months or years Great discretion has to be exercised in interpreting the test In some countries 20–30 per cent of the population may react positively to it It may be of value in survey work, but its use in the diagnosis of chronic brucella infection in the complete absence of other supporting laboratory findings should generally be discouraged It is well to remember that, particularly in persons who have been previously exposed to brucella infection the intradermal injection of the test antigen may be followed by the appearance of circulating antibodies"

The W H O committee on brucellosis believe that the intradermal test should not stand alone as supporter of the diagnosis

As to the *significance of a fourfold rise in titre after injection* of brucellin, we have seen no convincing evidence to justify Dr Wallis' interpretation Brucellin, like any other antigen, produces antibodies *the amount produced is—to judge* by experience with such things as T A B—very variable If the patient has had a previous infection—i e, has a positive *brucellin reaction—the titre will rise even higher than it will* in a virgin, and in the circumstances we feel that Dr Wallis places too much reliance on this serological reaction in making a *diagnosis* That was one reason why we described his conclusions as "dogmatic"

Re-examining the 35 case-histories in Dr Wallis' book, we would say that half are probably brucella infections, and *of the rest, some may be psychosomatic* ailments and some P U O s—and there are many causes of pyrexia in children about which we know little or nothing Dr Wallis' view seems to be that once a child has had a brucella infection any future vague illness is the same thing —ED L

HYPNOSIS AND UNREGISTERED PRACTITIONERS

Dr A A MASON, secretary, British National Division, International Society for Clinical and Experimental Hypnosis, writes

"*I have been approached by Dr Ainslie Meares, the Australian president of the society, and Dr H Grant-Whyte, a member of the South African Medical and Dental Council, both of whom are investigating the problem of lay hypnotists and the possible harmful effects which can be caused by the use of hypnosis by unqualified practitioners Dr Grant-Whyte has approached the Minister of Health in an attempt to get legislation in South Africa along the lines of the British Hypnotism Act, 1952, and also in an attempt to restrict the practice of unregistered and untrained persons It would be of great assistance to both these doctors to have available all the details of harmful effects which have followed the use of hypnosis by unregistered practitioners, and indeed if sufficient evidence is present it could stimulate similar action in this country I should be grateful, therefore, if any doctors who have evidence from their own practice of patients suffering harm following the use of hypnotism by unqualified practitioners could communicate the details of such cases to me at 24, Avenue Road, Regent's Park, London, N W 8 Of course, I need hardly assure the doctors and their patients that this matter will be treated in the strictest confidence*"

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[1] Wilson, G S, Miles A A Topley and Wilson's Principles of Bacteriology and Immunology London, 1955

Parliament

Handicapped Refugees

In the House of Lords on Feb 2 Baroness **Elliot of Harwood** asked if we could not mark World Refugee Year by admitting further immigrants into this country The appeal for money was being very successful and the target of £2 million would be exceeded. About £125,000 had been already allocated for rehousing outside the camps in Austria, Germany, and Italy large families and old and infirm people, both groups which were difficult to move to other countries £5000 was to be used for medical advice and to make a survey of people who had been many years in camp and whom it was difficult to take straight out and put into the world.

But the greatest stumbling-block to clearing the camps was the difficulty of resettling the handicapped refugees They were brought before tribunals and turned down because of illness or suspected tuberculosis and they and their families had to remain in camp In November the Government had given permission to bring in 210 handicapped refugees and their families But there was still a great need for us to be more generous about handicapped refugees The most recent figures showed that the number of handicapped refugees in camps is 10,000, comprising families of which one member is handicapped, and the number outside camps is 17,850 Of course, only a small proportion of handicapped refugees would want to come here Some of them wanted to be settled in the area in which they had been working or had been educated, and many wanted to go to the New World to get away from European problems But we could still take more here, and she asked the Government to consider altering slightly some of the terms under which people were brought here, and to be a little more generous, possibly, in statutory help for families should they by any chance fall again into difficulty after some years or not be in full employment.

Lord **Shackleton** pled for a more liberal application of some of the regulations He thought that experience was beginning to show that some health regulations were completely pettifogging—for example, the unwillingness to admit people who had had tuberculosis, who had been cured, and were now living useful lives He thought that we were putting unnecessary obstacles in the way, and in the process we and other countries had created great unhappiness

Lord **Amulree** agreed that it was a terrible thing if one member of a family which was acceptable here was found to have tuberculosis Until quite lately that was an absolute bar to their admission. We all knew that in this country tuberculosis, particularly of the chest and lungs, was, to a large extent, a curable disease Why were we so frightened of admitting people with this disease when there were facilities for treatment and good prospects of cure? He thought it improper that the Government would accept financial responsibility at no time for these unfortunate people One could see that for the first few years they were here they should be supported by voluntary bodies, but it was expected that most of them would obtain jobs and settle down to become perfectly good, reputable, and productive citizens of this country Why voluntary bodies who had money should be forced to keep sums aside in case these people fell on evil days in ten, twenty, thirty, or forty years' time he did not understand, and he trusted the Government would see their way to making these people eligible, when they came here as refugees, for the ordinary kind of benefits that a person living in this country would expect to obtain. The sum could not be large, but it was a very big sum for the voluntary organisations to have to put aside and tie up

Baroness **Swanborough** said that the family unit was always of paramount importance When a family was not only a family, but was the only asset that a small set of people possessed, it assumed very special proportions indeed She felt that we should do our utmost to preserve the family in its entirety The handicapped refugee families had been faced with years and years of misery in order not to break up their own unit. Because of a brother with tuberculosis, or a mother with cancer, or a small child who, through a brain injury, could never be a normal child, a whole family had lived all these years in a dreadful and unhappy way

Government regulations, framed meticulously by men and women of good will but of chairbound experience, had forbidden the entry into various countries of people with disabilities, specified diseases, and handicaps The debate had still ignored the fact that we were being allowed to bring into the country only people with handicaps that could be cured. She hoped that the Government would permit the entry within each family of a diseased or an incurable person who, despite the fact that he or she could not recover, could be looked after by his own family

The Marquess of **Lansdowne** said that he had listened to the debate with sympathy but he felt that we should remember that a quarter of a million people had been received into this country, and that 1 in every 200 of the people of the United Kingdom at the present time had been refugees 21 tuberculosis refugees had lately been admitted to the country, but it was correct that so far the regulations allowed only for curable cases He believed that that attitude might be very sympathetically considered by the Department concerned. Wherever it was economically possible, the Government would continue to do everything in their power to unite families Where there was a refugee settled in this country and earning money, members of the family were already allowed to come in. He believed that both the Home Office and the Ministry of Health tried to view this problem in a sympathetic way A further survey of handicapped refugees was shortly to be made. He believed the opening of the gates to the handicapped refugee was an important achievement.

Public Health Laboratory Service Bill

In introducing this Bill on Feb 4, Viscount **Hailsham** explained that the P H L S had been started shortly before the late war by the Medical Research Council at the request of the Committee of Imperial Defence Its original object was to provide a defence against possible enemy use of bacteriological warfare and against outbreaks of epidemic diseases In the event, the service was not used to deal with any major emergency of this kind On the other hand it came to be used by medical officers of health as a valuable aid to their ordinary work. Only in the areas of some of the larger local authorities had any such service previously been available. Indeed, the main reason for creating the service had been the inadequacy of the arrangements before the war for public-health bacteriological work. Thus, it came about that a service which had been designed for an emergency became an indispensable part of normal peace-time administration. It was therefore decided after the war to maintain it as part of the regular machinery for the diagnosis and control of infectious diseases The M.R C had continued to administer it as agents for the Minister of Health.

The P H.L S at present consisted of a central laboratory, 8 regional laboratories, and 51 area laboratories There were several special reference libraries, some at the central laboratory and some in other institutions The service was considered now to be fully developed, and no increase in the number of laboratories was planned The staff numbered 1068, of whom 126 were medically qualified The annual cost of the service was about £1,262,000

The M.R.C had for some time been anxious to divest themselves of responsibility for the service, and to substitute a permanent organisation responsible to the appropriate executive department for what was always an anomalous and temporary arrangement The work of the P H L.S was really peripheral to the M.R C's interests, for they were mainly concerned with research, while the service, though scientific, was largely routine and research was included only as a secondary function. There was some inconvenience in the anomaly that the M.R.C. were responsible for their normal activities to the relevant Privy Council committee, and for the P H L.S to the Minister of Health The position was also somewhat embarrassing for the M.R.C. as employers of labour The level of remuneration of their own staff was related to that of the staffs of universities The remuneration of the P H L S staff was related to that of staffs of hospitals in the National Health Service

The executive work of the P H L S had remained with the M.R.C 's headquarters staff, but the ordinary work of the Council and of their headquarters staff had continued to grow, so that it had now become necessary for the P H.L S to be given its own administrative machinery as soon as possible so as to release the headquarters staff of the M.R.C Accordingly, it was decided to introduce this Bill which would enable the Minister of Health to administer the service through a new Public Health Laboratory Service Board which he would appoint.

The board would be a separate entity, with legal status, and it would employ staff and hold property in its own name It would be analogous to a regional hospital board—that is to say, it would administer the service as the agent of the Minister It would be appointed by the Minister and its staff would not be Civil Servants It would be subject to the directions of the Minister, whose control of the service would thus remain more or less as at present.

The board would consist of a chairman and one other member, both medically qualified, two members appointed after consultation with the M.R C, two members with experience as bacteriologists, two members who were medical officers of health of local authorities, and two members with administrative experience

Lord Taylor described the P H L S as a kind of national medical Scotland Yard It differed only in that it had its peripheral units scattered all round the country and did not have to wait for a county police force to call it in It did, however, have to be called in by somebody, and the people who called it in were medical officers of health, hospitals, or local doctors One great feature of the service was that staff had always been available for personal consultation. They had come out to see cases, investigate problems on the spot, and help doctors with any kind of epidemiological problem.

The P H L S had also done an immense amount of research, and he was a little sorry to hear Viscount Hailsham say that the bulk of its work was routine and that it was not primarily a research organisation. Lord Taylor hoped that this transfer of functions would not entail any lessening of the research activities of the service The service had put Britain in the forefront of bacteriology and epidemiology The World Health Organisation had recognised the central laboratories of the service at Colindale as the World Influenza Centre It had also a virus reference library, a mycological reference library and an air hygiene unit It had an epidemiological research unit at Cirencester run by a part-time general practitioner On the purely bacteriological side the service maintained centres which concerned the whole of Europe and the Commonwealth for serological typing, particularly of salmonella and dysentery organisms Research ranged from bacteriological structure and metabolism to such practical questions as the design of operating-theatres and the bacteriology of public telephones and iced lollipops

Viscount Hailsham had also mentioned that the service was primarily linked with the medical officers of health Lord Taylor believed that it was also linked, perhaps more closely than was generally realised, with the hospital services In some places the public-health laboratory functioned as a general-hospital bacteriological laboratory, doing the routine bacteriology for that hospital and for the general practitioners as well as its own specialised work on milk, water, shell-fish, and ice-cream In other places it did specialised work only It had been suggested that the right thing would be to make the P H L S part of the regional hospital board service But Lord Taylor was sure that the decision taken by the Government was the right one The service should be kept as an entity, for bacteria knew no regional boundaries Moreover, there must be a central reference organisation, if these germs and viruses were to be identified in the increasingly difficult varieties in which they occurred.

Turning to the membership proposed for the new board, Lord Taylor said that he could see no reason for the stipulation that the chairman should be medical It was widely believed in the P H L S that the intended chairman might be the chief medical officer of the Ministry of Health Lord Taylor thought this a bad idea, because the chief medical officer was an exceedingly busy person and because the board should have an autonomy, a vigour, and a life of its own. It should be the servant of the Minister and subject to his general direction, but it should bat on its own wicket and not be tied to the Ministry The job of chairman called for someone who would give a good deal of time to it. 40 or 50 laboratories were scattered about the country If the chairman went round and saw every laboratory once a year it would be for the good of the staff. Lord Taylor regretted that there was no representative of the hospitals, though the service was closely linked with the hospitals, or of the general practitioners, though the general practitioners were exceedingly interested in the kind of research which the service did. He was also disappointed that there was no representative of the staff on the board.

Lord Amulree suggested that, as the board would work closely with the regional hospital boards, it might not be a bad idea to have on the board one of the senior medical officers who advised the hospital boards He, too, hoped that there would be some representation of the hospital service and general practice Another important point was that there should be one lay member

Viscount Hailsham agreed that to keep a service alive it was necessary to include research in its activities, and the P H.L.S 's research activities were important and creditable It was mainly for that reason that it was proposed that two members of the board should be appointed after consultation with the M.R C The composition of the board would probably be considered on the committee stage of the Bill Though the schedule did not contain a direct reference to a hospital representative, a number of medically qualified people would have to be appointed to the board, including bacteriologists and others, and he would have expected to find that the board contained names which came from the hospital service

Powers of Subpœna

On Feb 2 at the end of the committee stage of the Professions Supplementary to Medicine Bill a Government amendment was carried to remove the power of subpœna from the disciplinary committees to be set up under the Bill. Miss Edith Pitt, parliamentary secretary to the Ministry of Health, explained that the Government thought that the subpœna provisions should be omitted until the Simonds Committee had reported. The matter could then be reconsidered. The Bill would still enable the disciplinary committees to administer oaths It was hoped that the Simonds report would be ready before the Bill left the floor of the House

QUESTION TIME

General Practitioners' Central Fund

Mr Barnett Janner asked the Minister of Health how much Exchequer contribution had been deducted annually from the General Practitioners' Central Fund since 1955, how it was computed, and what was the relationship between the Exchequer contribution annually deducted from the Fund and the employers' contribution to the National Health Service compulsory superannuation scheme, and how he proposed to increase the employers' contribution so as not to reduce the sum to be distributed to general practitioners Mr Walker Smith replied The amount of the Exchequer superannuation contribution deducted from the Central Pool is the aggregate of the employers' superannuation contributions paid by the executive councils for the general medical practitioners with whom they are in contract The amounts involved were, for Great Britain

	£
1955–56	3,529,607
1956–57	3,569,494
1957–58	3,809,181

The superannuation position of practitioners cannot be considered further until the Report of the Royal Commission on Doctors' and Dentists' Remuneration has been received and considered I have, however, given an assurance that the supplementary employer's contribution which is being introduced to help liquidate the deficiency in the health service superannuation scheme will not have the effect of reducing the current net remuneration of general practitioners The detailed method of achieving this has still to be discussed with the profession.

Mr JANNER In considering this matter, will the Minister take into account the fact that the proportion which is being deducted, which is 8%, was given as 2% less by the actuary in 1955? In view of that, will he refund to the general practitioners the loss they have incurred thereby? Mr WALKER-SMITH· I do not think that that point arises The general situation which the hon. Gentleman wishes to safeguard is really dealt with in the penultimate sentence of my answer

Lay Hospital Staff

Dr A D D BROUGHTON asked the Minister the number of personnel, other than medical and nursing staff, employed in hospitals in England and Wales when the National Health Service came into operation in July, 1948, and the number at the latest convenient date Mr WALKER-SMITH replied In *round figures 197,000 at the end of 1948 and 250,000 at the* end of 1958 This includes professional, technical, works, maintenance, domestic, administrative, and clerical staff

Preludin (Phenmetrazine)

Mr MARCUS LIPTON asked the Home Secretary whether he had now received the report of the Poisons Board on 'Preludin', and whether he would now ban the sale of this drug without medical prescription.—Mr R A. BUTLER replied I have now received from the Poisons Board a report concerning a recommendation that a number of substances including preludin should be supplied only on prescription Subject to the consideration of any representations by those concerned, I propose to accept this recommendation and to give it effect as soon as practicable

World Refugee Year

Mr D E C PRICE asked the Home Secretary whether, in pursuance of the support of the World Refugee Year, he would admit another 1000 refugees to this country before Easter—Mr R. A. BUTLER replied Arrangements are being made in consultation with the United Kingdom Committee of the World Refugee Year, to ascertain the number of specially handicapped refugees who wish to come to this country and can be adequately sponsored by the voluntary organisations I shall consider the matter further when this information is available

Medicine and the Law

A Difficult Patient

SECTION 172 of the Public Health Act, 1936, dealing with precautions against exposure of the public to infectious diseases, sets out the conditions under which action may be taken to restrain infectious persons who refuse to accept precautionary measures This section of the Act was reluctantly invoked in Oxford last week to send to hospital for three months a woman of 52 who was known to have had pulmonary tuberculosis for twelve years

In April, 1948, after a hæmoptysis, she was found to have pulmonary tuberculosis with a probable cavity, but she refused to attend the chest clinic. She was offered a bed in hospital at any time convenient to herself but again refused. In July, 1948, she was found to be pregnant. Home conditions were very bad, and 4 adults and 2 children were occupying one room in a basement, so the family was ultimately rehoused in August, 1949 During this time repeated requests to attend the chest clinic were ignored. On one occasion she promised to attend if transport was provided, but an ambulance called three times without success Nothing further could be done, and the family was removed from the chest-clinic register

In August, 1951, another attempt was made to get her to the clinic, but it failed. Finally in March, 1954, she became very ill and she was admitted to hospital as an emergency Her sputum was loaded with tubercle bacilli and she had gross bilateral tuberculosis She remained in hospital having chemotherapy for three months, and then discharged herself against advice. She still had extensive and very unstable cavitated disease with a positive sputum, but there had been definite improvement. One of her children had phlyctenular conjunctivitis and was under care for several years Her other child also had primary tuberculosis, for which his mother refused hospital treatment.

After her discharge, there was a period of intermittent observation at the clinic and evidence of some improvement in her tuberculosis In September, 1954, she described symptoms which may have been due to drug intolerance, and streptomycin was withdrawn, although she was supposed to continue on P.A.S and isoniazid. In December, 1956, laryngeal-swab culture was positive for tubercle bacilli Further attempts, both by the clinic staff and by the medical officer of health, to get her to attend during 1957 were unsuccessful. At the end of 1958 it was thought that she was working in a canteen. In January, 1959, she was brought to the clinic by the chief public-health inspector in his car Bronchial lavage gave a positive culture for tubercle bacilli, which showed normal sensitivity to anti-tuberculous drugs X-ray examination showed extensive fibrotic disease which had not spread since November, 1956 She maintained that she had had chemotherapy ever since she last attended the clinic, but this was not confirmed by the doctor she named Last December bronchial lavage was again positive and radiologically the disease had extended

It was clear that she was infectious to other persons, that she would accept treatment only under duress, and that her promises to carry out treatment at home were quite unreliable. On Feb 4 the Oxford magistrates granted an order to Oxford City Council that she should be taken to the Osler Hospital for three months

We are indebted to Dr F Ridehalgh for supplying this information

Obituary

EILEEN MARY HICKEY

M D, B Sc Belf, F R C P I, D P H

Dr Eileen Hickey, who died on Feb 3 at her home in Belfast at the age of 75, was distinguished both as a physician and as a member of the Parliament of Northern Ireland

In her early life she entered the Civil Service, and it was not until she was in her early thirties that she decided to qualify in medicine She returned to Belfast and studied at Queen's University Her student career was marked by enthusiasm and by impatience to be qualified, and also by a positive enjoyment of the written examination which amazed her more usually pen-tied contemporaries She graduated M B with first-class honours in 1921 and two years later obtained the M D with a gold medal Her career as a physician was based on the Mater Infirmorum Hospital in Belfast, and she became senior physician and a member of the board of governors She examined in medicine at the university, was for many years a member of the senate, and was the first woman to be elected president of Queen's Graduates Association

A H B writes

"Eileen Hickey had a ready pen and spoke fluently and entertainingly It was no surprise to her fellow graduates when she was returned in 1949 as one of the four members representing the university in the Northern Ireland Parliament. She was returned as an Independent in a Parliament where politico-religious feeling ran high. She was again returned in 1953, but owing to failing health did not seek re-election in 1958

"She had many outstanding qualities Among them were a great sense of responsibility in everything she undertook and a deep sympathy for old people Her indignation was easily aroused on behalf of any person or cause that she thought unfairly treated She was a bonny fighter and a most staunch friend She worked hard for the cause of old people's homes when she was a member of the Council of Social Service in Northern Ireland, and, after the late war, she organised the sending of parcels to refugees and others impoverished by their war-time experiences She had a great love of gardening and of flowers

" She faced with fortitude her years of declining health and did not allow herself the indulgence of self-pity Her Church was very real to her and was a support and an abiding interest. She will be remembered by her university as a great character, and by her friends for her lively wit, dauntless spirit, and many acts of great kindness "

RAYMOND EBENEZER APPERLY

MRCS, FFARCS, DA

Mr Raymond Apperly, consulting anæsthetist to the Middlesex Hospital, London, died on Jan 29 at Evesham, at the age of 76

He was born in Stroud, Gloucestershire His father, Mr Ebenezer Apperly, L D S, had been a dental student at the Middlesex Hospital, and in due course Raymond, following what was becoming a family tradition, joined the medical school He qualified in 1907, and after holding house-posts at the Middlesex he was appointed anæsthetist to the Hospital for Sick Children, Great Ormond Street. In 1910 he joined the anæsthetic department at the Middlesex Hospital and later became lecturer in anæsthetics at the medical school In 1931 he succeeded Dr Herbert Charles as senior anæsthetist He took the D A in 1935 and was elected F F.A R C.S in 1948

H P C, who was a student with Apperly nearly sixty years ago, writes

"Raymond Apperly was a cheerful, friendly soul, popular alike with men, women, and children He had an extensive private practice, as I discovered if he was ill To give an anæsthetic to a patient who had already been sent to sleep by Apperly was not easy, for their disappointment was often so evident. One Saturday, years ago, the school doctor in Sussex phoned that my son had an acute appendix which should come out that day when he arrived by ambulance At 5 P.M Apperly appeared with the surgeon Some time later I found out that he was spending the day at Lancing with his son but had cut it short to help a friend. Such was the man. A delightful colleague who will be remembered with affection by the old brigade "

Mr Apperly leaves a widow, a daughter, and a son who is in practice at Evesham

ALEXANDER HUGH DICKSON SMITH

MC, TD, MB Edin, DL

Dr Smith, who died on Jan 31 at the age of 69, spent many years in practice in his native Llanelly and played a large part in the settlement of the " Llanelly dispute " of the mid '30s

He was educated at Llandovery College and the University of Edinburgh, where he qualified in 1914 The same year he joined the R.A M C and went to France, where he became attached to the Guards Division He was awarded the M C for conspicuous bravery in 1917 He served later with the 3rd and 29th Divisions and finished his war service in India On his return to Llanelly he at once entered general practice Soon afterwards he joined the staff of Llanelly and District Hospital He did most of the surgical work there and became the first honorary radiologist to the hospital

As a member of the Territorial Association he was sent on the outbreak of the late war to France with the rank of lieut-colonel He returned from France in 1940 and thereafter acted as O C. to units in Western Command At this time he gave up his general practice, but he remained extremely active in medical affairs in South Wales he was chairman of many committees, including the Ministry of Pensions boards for Swansea and Carmarthenshire, the committee under the Disabled Persons Act, and the Carmarthenshire panel, insurance, and executive committees He was high sheriff of the County of Carmarthen for 1944 and 1945, and deputy lieutenant in 1952

He married Joan Margaret, daughter of the late Dr Hugh John She survives him, with their daughter

Diary of the Week

FEB 14 TO 20

Monday, 15th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P.M Dr Brian Ackner Diagnosis of Organic Confusional States
GUY'S HOSPITAL, S E 1
5.30 P.M Prof Douglas Hubble Virilism
UNIVERSITY OF ST ANDREWS
4 P.M (Queen's College, Dundee) Prof R. B Hunter Virilising Syndromes—Problems of Intersex

Tuesday, 16th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C.2
5 P M Prof Arnold Sorsby Optical Components During the Growth of the Eye
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M (London School of Hygiene and Tropical Medicine, Keppel Street, W C.1) Prof C. H Gray Non-pancreatic Aspects of Diabetes Mellitus
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M Dr Jack Suchet Appraisal of the Results of Treatment of Infertility
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5.30 P.M Dr G A D Gordon Ultrasonic Rays in Neurosurgery
OSLER CLUB OF LONDON
8 P.M (Wellcome Building, Euston Road, N W 1) Dr Kenneth Dewhurst, Prof G E Trease Thomas Dover (born 1660)
LEEDS NEUROLOGICAL SCIENCIES COLLOQUIUM
5 15 P.M. (General Infirmary at Leeds) Dr J W D Bull Radiological Investigation of Strokes
UNIVERSITY OF ST ANDREWS
5 P.M (Queen's College, Dundee) Prof Adam Patrick Symptoms of Diabetic Coma a Retrospect.

Wednesday, 17th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 15 P.M. *General Practice* Dr R. A P Paul, Mr H G Hanley, Dr R. I. Bodman Prostatectomy—Early or Late?
INSTITUTE OF DERMATOLOGY, Lisle Street, W C.2
5.30 P.M. Dr Henry Haber Pigmented Lesions of the Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W.3
5 P M Mr J R Belcher Surgical Treatment of Lung Cancer
EUGENICS SOCIETY
5 P.M (Manson House, Portland Place, W 1) Dr Eliot Slater Galton's Heritage. (Galton lecture)
UNIVERSITY OF ST ANDREWS
2.30 P.M (Queen's College, Dundee) Dr J M Stowers Investigation of Hypoglycæmic Agents

Thursday, 18th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M Dr M O Skelton *Pathological Conditions of the Pulmonary Tissues* (Erasmus Wilson demonstration.)
UNIVERSITY OF LONDON
5.30 P.M (King's College, Strand, W C.2) Dr Harris Isbell (Bethesda) Pharmacology of Opiate Addiction
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P.M (London School of Hygiene and Tropical Medicine.) Dr E. M. Vaughan Williams Relations Between Contractions and Intracellulary Recorded Potentials in Cardiac Muscle
ROYAL SOCIETY OF MEDICINE
4 45 P M *Dermatology* Dr W Frain-Bell Grenz Rays in the Treatment of Benign Dermatoses
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, Manson House, 26, Portland Place, W 1
7.30 P.M Dr T F Davey Recent Chemotherapeutic Work in Leprosy
BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W 1
8 P.M Dr Sydney Blackman Rotational Tomography of the Face.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8 15 P.M (11, Chandos Street, W 1) Dr Alick Isaacs Prospects for a Viral Antibiotic.
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Hospital, Oxford
8.30 P.M Mr Denis Browne Orthopædics of the Fœtus
UNIVERSITY OF ST ANDREWS
5 P M (Queen's College Dundee) Dr C Kerr McNeil Orthopædic Principles in the Treatment of Lip and Palate Clefts

Friday, 19th

UNIVERSITY OF LONDON
4 45 P.M (St Bartholomew's Hospital, E C.1) Prof. J Loewenthal (Sydney) Contributions to Surgical Research.
ROYAL SOCIETY OF MEDICINE
5.30 P.M *Epidemiology and Preventive Medicine* Dr J D Cottr The Role of the World Health Organisation in Epidemiology
8 15 P.M *Radiology* Mr P T Savage, Mr S L. Strange, Dr Gord Osborne, Mr N R Barrett, Dr Brian Creamer, Dr J W Pier Dysphagia.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M Prof A S Johnstone Hiatus Hernia
4 P.M Dr Fraser Roberts Medical Genetics
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C.1
3.30 P.M Mr W D Doey Foreign Bodies in the Ear, Nose, and Thro
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W C.1
4.20 P.M Dr Macdonald Critchley History of our Conception as to t Origin of Language in Man. (Part I)
PLYMOUTH MEDICAL SOCIETY
8.30 P.M (Freedom Fields) Discussion Medicine and the Law

Notes and News

WORLD HEALTH ORGANISATION

THE executive board ended its session on Feb 1 The proposals of the director-general, Dr M G Candau, for W H O 's 1961 programme and regular budget of $18,569,620, were unanimously recommended to the Health Assembly which opens in Geneva on May 3 The board approved steps taken towards the building of a new headquarters for the Organisation in Geneva. On a site not far from the Palais des Nations, this will cost about 40 million Swiss francs, of which 20 million is to come from the Swiss Federal authorities in the form of an interest-free loan, and 10 million is to be made available by the Republic and Canton of Geneva, which is also giving the site The architectural competition closes on April 14

Only about 1 million dollars is now needed to finance W.H.O 's share of the costs of malaria eradication for 1960, but $6 4 million is needed to ensure continuation of the work in 1961

Figures released on Jan. 29 show that the world incidence of plague was as low last year as in 1958, fewer than 300 cases of human plague were officially reported in ten countries of Africa, America, and Asia (outside continental China) The occurrence of " accidental " single cases (in the United States of America and Madagascar) and of small foci in areas which had been apparently free from human cases for one or more years (in Northern India and in the Union of South Africa) indicates that the infection is maintained among rodents in wide areas of the three continents Burma notified the highest number of cases (98)

Cholera incidence in 1959 was unusually low in India, and, in spite of the presence of the disease in Thailand and its considerable increase in East Pakistan during October and November, fewer than 42,000 cases were officially reported in Asia (excluding China), compared with about 95,000 in 1958 and 64,000 in 1957 " In India the situation was probably the most favourable on record Less than 14,000 cases were provisionally notified against 67,000 reported in 1958 "

SUPPLEMENTARY ESTIMATES

THE supplementary estimate for the National Health Service in the current financial year [1] shows an increase for England, Wales, and Scotland of £25,600,000, bringing the total net cost to £562 million. Of the additional sum £15 million goes to the revenue account of hospital boards, mainly to meet salary and wage increases, £6 million to the pharmaceutical services because of an increase in the number of prescriptions and higher average costs per prescription, and £1½ million to meet the increased demand for poliomyelitis vaccine

O & M

FIRST reaction to the latest report [2] by the Hospital Organization and Methods Service may be that it is all obvious and simple so it is, but there is no doubt that it is also a necessary and sad commentary on some aspects of the National Health Service The report concerns the activities of chest clinics, including the design of an outpatient appointments system, the efficient use of the time of staff and patients, and the keeping of medical records Chest clinics are used merely as an illustration. They are well chosen for this purpose, for they are often relatively small self-contained units handling large numbers of " new " and " old " patients, and therefore easy and profitable to study The fact that they are the subject of this report does not mean that they are either better or worse organised and run than any other branch of the N.H S

The instructions for studying the problem of efficient flow of patients in a clinic are clearly expressed and easy to carry out. It is almost a shock to see a whole-page diagram whose sole purpose is to illustrate that the rate of flow is determined by the speed of the slowest process The same applies to the movements of armies and was discovered long ago But if this and similar " rules " were widely acknowledged and acted on there would be no need for O & M surveys The report concludes

> " The great bulk of matters dealt with here is concerned with efficiency of a fairly mechanical kind. It is recognised that this efficiency ranks only second in importance to the standard of medical and nursing care which is given to the patients These two aspects are not, as is sometimes assumed, conflicting, but complementary Medical care is hampered if case-notes go astray, and medical skill of the highest quality is wasted if the patients become disgruntled and do not come to take advantage of it If, on the other hand, medical skill is practised in an environment of orderliness, if waste of time and effort are eliminated, and if the general, as distinct from the purely medical, well-being of the patients is secured, the maximum benefit will be derived from the services provided."

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names

Approved name	*Other names*
Bamethan	2-*n*-Butylamino-1-*p*-hydroxyphenylethanol Vasculit is the sulphate
Bendrofluazide	3-Benzyl-3 4-dihydro-7-sulphamoyl-6-trifluoromethyl-benzo-1 2 4-thiadiazine 1 1-dioxide Aprinox
Carbolonium Bromide	Hexamethylenebis (carbamoylcholine bromide) Imbretil
Carisoprodol	2-Carbamoyloxymethyl-2-*N*-*iso*propylcarbamoyloxypentane
Cetylpyridinium Chloride	1-Hexadecylpyridinium chloride Ceepryn
Cyclandelate	3 3:5-Trimethyl*cyclo*hexyl mandelate Cyclospasmol
Cyclophosphamide	2-[Di-(2-chloroethyl)amino]-1-oxa-3-aza-2-phospha*cyclo*hexane 2-oxide Endoxan, Cytoxan
*Dextropropoxyphene	*a*-(+)-4-Dimethylamino-1.2-diphenyl-3-methyl-2-propionyloxybutane Darvon is the hydrochloride, Doloxene is the hydrochloride
Dimethoxanate	2-(2-Dimethylaminoethoxy) ethyl phenothiazine-10-carboxylate
Diphenadione	2-Diphenylacetylindane-1.3-dione Didandin, Dipaxin, Oragulant
Diphenoxylate	Ethyl 1-(3-cyano-3.3-diphenylpropyl)-4-phenyl-piperidine-4-carboxylate
Disulphamide	5-Chloro-2 4-disulphamoyltoluene Disamide
Heptabarbitone	5-Ethyl-5-*cyclo*hept-1 -enylbarbituric acid Medomin
Nialamide	*N*-(2-Benzylcarbamoylethyl)-N -*iso*nicotinoylhydrazine Niamid
Phenazocine	2 -Hydroxy-5 9-dimethyl-2-phenethyl-6 7-benzomorphan
Phenprocoumon	4-Hydroxy-3-(1-phenylpropyl)coumarin Marcoumar
Salazosulphadimidine	4 -(4 6-Dimethylpyrimid-2-ylsulphamoyl)-4-hydroxy-azobenzene-3-carboxylic acid Azudimidine
Sulphaphenazole	5-*p*-Aminobenzenesulphonamido-1-phenylpyrazole Orisulf
Tetrahydrozoline	2-(1.2.3 4-Tetrahydro-1-naphthyl)imidazoline Tyzanol is the hydrochloride
Trimustine	Tri-(2-chloroethyl)amine Trillekamin

* Replaces the approved name propoxyphene for α-(+)-4-Dimethylamino-1·2-diphenyl-3-methyl-2-propionyloxybutane.

Proprietary name	*Approved name reference*
Aprinox	Bendrofluazide
Azudimidine	Salazosulphadimidine
Ceepryn	Cetylpyridinium Chloride
Cyclospasmol	Cyclandelate
Cytoxan	Cyclophosphamide
Darvon	Dextropropoxyphene
Didandin	Diphenadione
Dipaxin	Diphenadione
Disamide	Disulphamide
Doloxene	Dextropropoxyphene
Endoxan	Cyclophosphamide
Imbretil	Carbolonium Bromide
Marcoumar	Phenprocoumon
Medomin	Heptabarbitone
Niamid	Nialamide
Oragulant	Diphenadione
Orisulf	Sulphaphenazole
Trillekamin	Trimustine
Tyzanol	Tetrahydrozoline
Vasculit	Bamethan

Association of Industrial Medical Officers

THIS Association is offering in 1961 a prize (50 guineas) for an essay from a member on research on occupational health. Further details may be had from the hon secretary of the Association, 47, Lincoln's Inn Fields, London, W C 2

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[1] 1959-60 Supplementary Estimates and Estimates for Revenue Departments H M Stationery Office 1960 Pp 171 9*s* 6*d*

[2] Chest Clinics Hospital Organization and Methods Service Reports, no 3 H M Stationery Office 1959 1*s* 9*d*

University of Oxford

Sir Lindor Brown, Jodrell professor of physiology at University College, London, has been appointed Waynflete professor of physiology in succession to Prof E G T Liddell, who is retiring under the age-limit

Sir Lindor, who is 56 years of age, was educated at the Boteler Grammar School, Warrington, and the University of Manchester, where in 1924 he took his B SC with honours in physiology and was awarded a Platt physiological scholarship The following year he took his M SC In 1928 he graduated M B , and in the same year he was appointed lecturer in physiology at the University of Leeds He worked there on gastric innervation with the late B A McSwiney and on transmission through sympathetic ganglia In 1934 he joined the scientific staff of the Medical Research Council, working in Sir Henry Dale's laboratory on transmission at nerve-endings by acetylcholine In the early years of the war he worked on military problems, spending some time in the laboratory at Lulworth In 1942, when the Royal Naval Personnel Research Committee was set up, he became its secretary, and until 1945 he was directing work in his own laboratory on underwater physiology, dealing particularly with problems affecting submarine crews and divers using self-contained gear He was appointed to the Jodrell chair in 1949 He was a member of the Medical Research Council from 1951 to 1955 and of the Advisory Council on Scientific Policy from 1956 to 1959 He has been successively secretary of the Physiological Society, an editor of its journal, and foreign secretary He was elected F R.S in 1946, and became biological secretary of the Royal Society in 1955 and a vice-president in 1956 He was elected F R C P in 1958 In 1947 he was appointed C B E , and in 1957 he was knighted

University of Cambridge

On Jan 23 the following degrees were conferred

M B , B Chir—A J H Nix
M B—*J D Allison, *John Farmer, D H Keeling, C J F L Williamson

* *By proxy*

University of London

Dr H O Schild, reader in pharmacology at University College, has been appointed to the chair of pharmacology at the college

Dr Schild took the degree M D Breslau in 1932 and joined the scientific staff of the Medical Research Council at the National Institute for Medical Research in London He has worked in the departments of physiology and pharmacology of Edinburgh University, and in 1937 he joined the staff of the department of pharmacology at University College, London In 1935 he took the PH D Edin and in 1950 the D SC Lond His published work includes studies on the principles of biological assay, drug antagonism, and an extensive series of papers on the mechanism of the anaphylactic reaction and histamine He is joint editor of the 1959 edition of *Applied Pharmacology*

Dr W F Widdas, reader in physiology at King's College, has been appointed to the chair of physiology at Bedford College

Dr Widdas qualified M B from the University of Durham in 1938 and has since taken the degrees of PH D and D SC of the University of London He held a senior lectureship in physiology at St Mary's Hospital Medical School before taking up his present post During the late war he served with the R A M C with the rank of major

Dr Hermann Lehmann, senior lecturer in chemical pathology at St Bartholomew's Hospital Medical College, has been appointed to the readership in that subject at the college

The title of reader in chemical pathology has been conferred on Dr G R Webster in respect of his post at Guy's Hospital Medical School

Royal College of Physicians of Ireland

At a meeting of the college on Feb 5, with Dr P T O'Farrell, the president, in the chair, the following were admitted to the licence and membership

Robert Carroll, D C Curtin, J P Duffy, J S Wright.

Royal Australian College of Physicians

The following officers of the college have been elected for 1960–62

President, T M Greenaway (Sydney), vice-presidents, F R Hone (Adelaide), H M Rennie (Sydney), E H Roche (Auckland), censor-in-chief, K B Noad (Sydney), hon treasurer, G B D Hall (Sydney), hon secretary, R L Harris (Sydney)

Royal College of Physicians of Edinburgh

At a meeting on Feb 2, with Dr A Rae Gilchrist, the president, in the chair, the following were elected to the membership

A L K Rankin, Raghunath Singh Hoon, I S Trotter, Bomullige Dilipkumara Dharmasena, *Mohd Hayat Zafar, K D* Coorey, Mary Cherian, R S Wells, *S J Surtees*, G P Lewis, D J Woods, W A G Roper, Ramji Singh, Sushil Kumar Mitra, Bhattarahalli Gururao Srinivasa *Murthy, Colin Protheroe, J C Maclaurin*, Prasanta Kumar Basu, Kandathil Mammen Cherian, Tin Ohn, Nabiha Hasan Rizavi, Krishna Kant Sinha, Roop Kishore Seth, Ma Hnin Yee, Kathleen A Irvine, G W Ferton, Francis Moran, Narayanarao Ambajeerao Jadhav, Freda M Paul, Ishau Sh'Aibu Audu, *Chinganezhath Krishnan* Ramachandran, Yip Chong Wong J S Fleming, Vetherednam Thuraisingham, F P Retief, J G Richards, Manasija Sarkar, L L Wilson, Kottaram Venkatachala Sarma Krishna *Das, Upamaka Brahmaji Rao*, F Po-Tun Fok, W E Ince, I T Draper, Sydney Louis, E S Paykel, Anupam Das Gupta, D F Scott

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the Faculty on Feb 1 with Mr Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship

Perinkulam Krishnaswami Ramaswami qua physician, Ratan Lal Agarwal, Alumootil David George qua surgeon

Lady Tata Memorial Trust

The trustees of this fund invite applications for grants, scholarships, and fellowships for research on blood diseases, with special reference to leukæmia

Programmes of research on any aspect of malignant disease which may throw light on problems of leukæmia will be considered and awards may be made to investigators of any nationality, working in any country where payment can be made Application forms may be had from the secretary of the (European) Scientific Advisory Committee of the Trust, Chester Beatty Research Institute, Fulham Road, London, S W 3 Applications must be submitted before March 31

Scottish Health Services Council

Mr John Dunlop has been appointed chairman of the council in succession to Prof G L Montgomery

International Congress on Alcohol and Alcoholism

This congress will be held from July 31 to August 5, in Stockholm Further particulars may be had from the congress secretary, Box 5071, Stockholm, 5, Sweden

Universities Federation for Animal Welfare

The annual general meeting of this Federation will be held on Tuesday, Feb 16, at 6 P M , at the Conway Hall, Red Lion Square, London, W C 1, when Major C W Hume will report on his recent visit to the conference of the Animal Care Panel in America At 8 P M there will be a brains trust

Surgeon Captain F P Ellis, of the Medical Department of the Admiralty, has been awarded £100 and a medal by the Chadwick Trust in recognition of his work during the last five years in promoting the health of Royal Navy personnel

Courses for candidates for the D M R.D and D.M R T , starting in October, are now being organised by the Faculty of Radiologists Further particulars may be found in our advertisement columns

The British Council for Rehabilitation and the University of St Andrews will hold a conference from March 29 to 31, at Queen's College, Dundee The subject will be rehabilitation—its industrial and social implications Further particulars may be had from the general secretary of the Council, Tavistock House South, London, W C 1

The North of England Otolaryngological Society will hold a meeting in Hull on Saturday, Feb 20, at 2 P M

Appointments

BRITAIN, ELIZABETH, M B Lond assistant M O , Brigg and Barton area of Lindsey
MCNEIL, N L., M B Lond , D O.M.S consultant ophthalmologist, Barnsley group of hospitals
MARSHALL, BARBARA S M , M B Birm assistant M O , Worcestershire
NICHOLSON, BASIL, M B Manc , D P H , D T.M & H assistant M O H and school M O , Gloucestershire
OCCLESHAW, J V , M.B , B.SC. Lpool, D M.R D consultant radiologist regional neurosurgical centre Walton Hospital Liverpool
OWEN, GORONWY, M B Wales consultant pathologist, Doncaster group of hospitals
WRIGHT, J T , D.M Oxon., M R C.P part time consultant physician, St. John s Hospital for Diseases of the Skin, London

The Lancet · Saturday 20 February 1960

A CLINICAL METHOD OF SSESSING THE RESULTS OF THERAPY IN THYROTOXICOSIS

J Crooks
M.D Glasg, M R.C.P, M R.C P E, F R.F.P S
SENIOR REGISTRAR IN MEDICINE

E J Wayne
M.D Leeds, F R.C P, F R.F P S.
REGIUS PROFESSOR OF PRACTICE OF MEDICINE

NIVERSITY DEPARTMENT OF MEDICINE, GARDINER INSTITUTE,
WESTERN INFIRMARY, GLASGOW

R A Robb
M.A., D Sc. Glasg, F R.A S, F R.S E
MITCHELL LECTURER IN STATISTICS,
IVERSITY DEPARTMENT OF MATHEMATICS, THE UNIVERSITY, GLASGOW

Thyrotoxicosis may be treated surgically, by radio-tive iodine, or by one of the antithyroid drugs Which- er method is chosen the clinician must decide whether not his treatment has been effective. His conclusions e based on the gradual disappearance of a number of normal symptoms and signs Different observers may tribute differing degrees of significance to these changes id for this reason it is desirable that the same person ould carry out the interview and examination at each sit. But even when this is practicable the observer may id it difficult to decide on the relative importance which ould be attached to different clinical features especially they are in conflict—for example, to a reduction in the egree of tachycardia combined with a failure to gain eight. That the inaccuracy inherent in a purely clinical sessment of the regression of the disease is real is shown y comparing the conclusion of Bartels (1945) that uobarbitone is 12 times more active in thyrotoxicosis than uouracil with that of Astwood (1945) who found it to be nly twice as active

The alternative method of following a patient's progress y repeated estimations of the basal metabolic rate 3 M R.) is time-consuming and inconvenient for the atient In addition it is necessary to allow for the effect f training, and because of the wide normal range the nethod is applicable only to groups of patients and the esults must be treated statistically Since diagnostic tests sing radioactive iodine give misleading results in a atient receiving an antithyroid drug this parameter of hyroid function cannot be used in assessing therapeutic esponse

We have approached this problem of assessing the esponse to treatment in a new way In a previous nvestigation we were able to allocate figures indicating he relative diagnostic value of the various symptoms and igns of thyrotoxicosis To do this we carried out an nalysis of their comparative frequency in patients with he disease and in normal individuals From these we lerived a total score which we called the diagnostic index nd which we have been able to show has about the same legree of diagnostic accuracy as estimations of the B M R, r the results of radioactive-iodine studies (Crooks et al 1959) By removing from the list of these diagnostic eatures of thyrotoxicosis those which are unaffected by reatment we have now constructed a therapy index which gives a quantitative measure of the response to treatment This paper describes our method We illustrate its application by comparing two antithyroid drugs, methylthiouracil and potassium perchlorate

Material and Methods

We first studied 40 thyrotoxic patients with diffusely enlarged thyroid glands and exophthalmos—that is to say, they formed a homogeneous group exhibiting classical Graves' disease

All were admitted to hospital and the diagnosis was confirmed by radioactive-iodine studies, including the 4-hour uptake of ^{131}I and the 48-hour plasma-protein-bound radioactivity B.M R.s and serum-cholesterol values were also estimated

The patients were allocated to two groups, one to be given methylthiouracil and the other potassium perchlorate Methylthiouracil was given in the doses we use routinely—namely, 200 mg three times a day for two weeks, followed by 100 mg three times a day Potassium perchlorate was given in a dose of 200 mg three times a day which is the dose originally used by Godley and Stanbury (1954)

Before treatment began, the patients were discharged from hospital and instructed to attend weekly At the first outpatient attendance they were examined by a standard routine Each subject was weighed in her clothes and asked to wear the same clothing on subsequent visits She was then instructed to lie down on an examination couch and was left undisturbed for 10 minutes The resting pulse-rate was counted for 1 minute and the presence or absence of the symptoms and signs shown in table I was recorded. The history was taken and the physical examination was carried out in the same way for each patient, the criteria for the identification of symptoms and signs being those laid down by Crooks et al (1959), except in the case of the pulse-rate where a resting rate higher than 85 beats per minute was scored as abnormal. Throughout the series all observations, with a few exceptions, were made by one of us (J C), whose observations in previous observer-variation studies involving the clinical features shown in table I did not differ significantly from those of 7 other experienced observers (Crooks et al. 1959)

Numerical values were allocated to each clinical feature (table I) on the basis of their diagnostic significance (Crooks et al 1959) except in the case of appetite increase and weight loss We had previously established that the combination of these two symptoms was of great diagnostic importance, and for the purpose of diagnosis each was rated +3 giving a value of +6 if both were present In the assessment of therapeutic response, however, the restoration of weight loss is of much greater significance than the return of the appetite to normal, and for this reason the rating for the symptom of weight loss was increased to +4 and that for increase of appetite reduced to +1 By adding the values obtained after the first outpatient

TABLE I—WEIGHTING FACTORS ALLOCATED TO THE SYMPTOMS AND SIGNS OF THYROTOXICOSIS

Thyrotoxicosis-therapy index

Symptoms	Score	Signs	Score
Dyspnœa on effort	+1	Hyperkinetic movements	+4
Palpitations	+2	Fine finger tremor	+1
Tiredness	+2	*Hands*	
Preference for cold	+5	Hot	+2
Excessive sweating	+3	Moist	+1
Nervousness	+2	*Resting pulse-rate*	
Appetite increased	+1	More than 85 per min.	+3
Weight decreased *	+4		

* For each 4 lb weight gain deduct 1 point.

TABLE II—CHANGES IN BASAL METABOLIC-RATES (ROBERTSON AND REID)

Patient no.	Potassium perchlorate: Initial (before therapy) %	Potassium perchlorate: Final* (after therapy) %	Patient no.	Methylthiouracil: Initial (before therapy) %	Methylthiouracil: Final* (after therapy) %
1	+75	+9	21	+22	−14
2	+27	−6	22	+71	−17
3	+20	+14	23	+45	−11
4	+17	+9	24	+27	+10
5	+21	+4	25	+51	+6
6	+28	+2	26	+84	−14
7	+32	−21	27	+71	−5
8	+8	−18	28	+36	−13
9	+67	+14	29	+51	−8
10	+76	−3	30	+23	−14
11	+10	+8	31	+42	+8
12	+60	+14	32	+71	−4
13	+16	+11	33	+17	−12
14	+26	−9	34	+41	+8
15	+33	−5	35	+15	+2
16	+17	−17	36	+47	+8
17	+12	+3	37	+46	−8
18	+20	0	38	+43	−2
19	+13	−12	39	+47	+1
20	+16	−1	40	+53	+1
Mean	+35.7	0.0 (S.D. 10.6)	Mean	+47.0	−3.9 (S.D. 9.2)

* Taken nearest to week in which the patient reached a therapy index of 5 or less.

attendance a total score, which we term the therapy index, was derived for each patient.

At the first outpatient visit treatment began and alternate patients were given methylthiouracil or potassium perchlorate. The patients receiving potassium perchlorate were instructed not to eat fish or iodised salt and to avoid medicines containing iodine.

At each subsequent weekly visit the procedure for ascertaining body-weight, resting pulse-rate, and the presence or absence of the clinical features of the disease was repeated. When a symptom or sign disappeared completely its value was deducted from the therapy index of the previous week. In the case of weight increase one point was deducted from the initial index for each 4 lb. of weight gained. In this way a fresh index was calculated weekly for each patient. B.M.R. estimations were carried out in all patients at two-weekly intervals. The technique used was that described by Crooks et al. (1958).

Complete remission of the disease or "cure" was taken to have occurred when the therapy index reached and remained within the range 0–5 for three successive weeks. The actual week of "cure" was chosen as that week with the lowest of the 3 values. This range was adopted since indices greater than 5 are obtained if two clinical features conventionally regarded as of high diagnostic significance are present simultaneously (table I). Strong confirmation that the range 0–5 indicates full control of the disease was afforded by the estimations of the B.M.R. (table II). Further confirmation was obtained by the observation that in patients who were satisfactorily controlled by antithyroid drugs, indices fluctuated within this range for long periods.

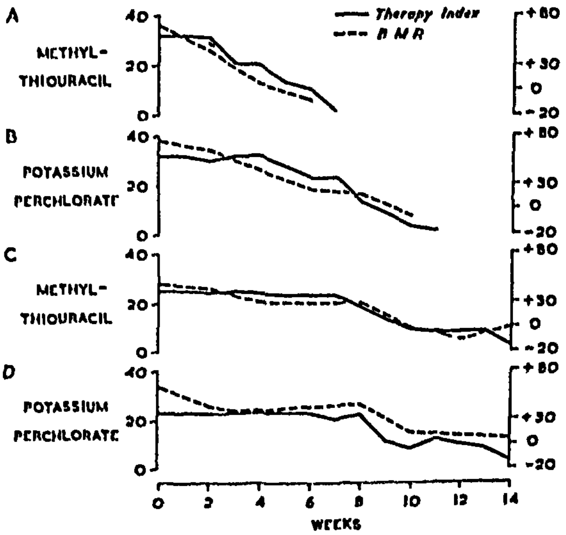

Fig. 1—Rate of change in the therapy index and the B.M.R. during treatment with methylthiouracil and potassium perchlorate (600 mg. daily). A and B show linear changes of the therapy indices with time. B and C show the delayed type of therapeutic response.

When the patient was euthyroid she was given maintenance doses of the drugs ranging from 50 to 150 mg. daily for methylthiouracil, and 200 to 400 mg. daily for potassium perchlorate. After 3 months maintenance therapy administration of the drugs was stopped. 14 of the 40 cases (series 1) relapsed and then formed a separate group (series 2). In this investigation patients acted as their own controls. The design was similar to that of the "cross-over" method used by pharmacologists for the biological assay of substances such as insulin. Thus 8 subjects of series 1 who had been given methylthiouracil, and who had relapsed when therapy was stopped, were retreated with potassium perchlorate. Similarly 6 subjects who had been treated with potassium perchlorate were retreated with methylthiouracil. The same dosage schemes for each drug were used in retreatment as in the initial treatment and the follow-up procedure was identical. Progress was checked by repeated estimations of the B.M.R.

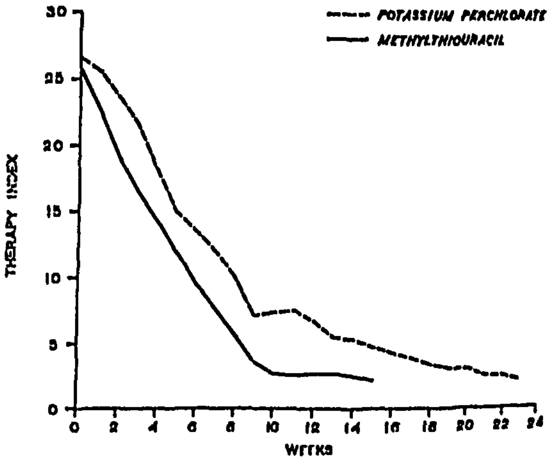

Fig. 2—Rate of change of the mean therapy index produced by potassium perchlorate and methylthiouracil in 2 groups of 20 patients (series 1).

Results

Series 1 (Time taken to "cure")

The number of patients reaching the level we have defined as "cure" at any given time is shown in table III. The mean time to "cure" of the 20 patients receiving methylthiouracil was 9.1 weeks, and the comparable figure for the 20 patients receiving potassium perchlorate was 13.1 weeks. These values are significantly different ($P < 0.01$). It can be seen from table III that in the group of patients receiving potassium perchlorate the longest time taken to effect "cure" was 23 weeks compared with 15 weeks for methylthiouracil. It also shows the larger number of patients receiving perchlorate who required long courses before "cure" was achieved.

Variations of Therapy Index with Time

Typical examples of the changes in the index during therapy are shown in figs. 1A (methylthiouracil) and B (potassium perchlorate). The associated changes in the basal metabolic rate plotted on the same figures show good agreement with the clinical method of assessment.

TABLE III—DISTRIBUTION OF PATIENTS IN SERIES 1 RECEIVING METHYLTHIOURACIL AND POTASSIUM PERCHLORATE (600 mg DAILY) SHOWING TIME TAKEN TO EFFECT " CURE "

Time to effect " cure " (weeks)	Methylthiouracil (no of patients)	Potassium perchlorate (600 mg daily) (no of patients)
3–4	1	
5–6	3	
7–8	4	5
9–10	10	3
11–12	1	4
13–14		3
15–16	1	
17–18		2
19–20		1
21–22		1
23–24		1
Total	20	20
Mean time to " cure "	9 1 weeks	13 1 weeks

In the case of both patients illustrated in these figures linear regressions of the therapy indices on time showed a significant fall in the values of the index with time This relationship was found to hold in 17 of the 20 patients treated with methylthiouracil. The remaining 3 patients were slow to respond to the drug, and the changes both in the therapy index and in the basal metabolic rate in this type of response are shown in fig 1c. The indices of all 3 patients, however, reached values of 5 or less in subsequent weeks Of the 20 patients treated with potassium perchlorate, 16 showed falls in the value of the index with time which were significant. In 1 of the remaining 4 patients the values of the index suggested that the reason for the non-significant fall was the absence of data on three occasions on which she defaulted. The remaining 3 patients did not respond to treatment until 6 weeks or more had elapsed and an example of this type of response to perchlorate is shown in fig 1D

Fig 2 shows the changes in the mean therapy index with time for each group of 20 patients The more rapid improvement in patients treated with methylthiouracil as compared with potassium perchlorate is clearly seen This method of comparing the effectiveness of the two drugs is, however, statistically unsatisfactory because of the two types of therapeutic response obtained with each drug For example the mean curves for both drugs show a uniform decrease in the value of the index for the first few weeks of treatment and the variations of the type shown in fig 1c and D are concealed. It was for this reason that we did not compare the effectiveness of the drugs by the rate of change of the therapy index but adopted the time taken to effect " cure " as the criterion of therapeutic response

Effect of Initial Values of the Therapy Index

A comparison between the initial values of the therapy indices and the times taken to effect " cure " showed that for the groups on either drug there was no significant correlation between these two variables In other words, the time taken to effect " cure " was uninfluenced by the initial degree of severity of the disease

Basal Metabolic Rate

The mean values of B M.R S in the patients of both groups of series 1 before and after therapy are shown in table II These do not exactly correspond to the times when the patients had reached the week of " cure " The reason for this discrepancy is that the values of B M R S were obtained at fortnightly intervals, whereas the therapy indices were obtained at weekly intervals For the 20 patients treated with methylthiouracil the mean value after therapy of —3 9 corresponds to a time 0 55 week before the week of " cure ", for the 20 patients on potassium perchlorate the mean value after therapy of 0 0 corresponds to a time 0 35 week before the week of " cure " 2 patients who received potassium perchlorate had B M.R.S below the usually accepted upper limit of the normal range but were thyrotoxic by all other criteria, including radioactive-iodine tests We have previously pointed out that this may occur and that in such cases the B M R falls with treatment (Crooks et al 1958)

At the beginning of treatment using methylthiouracil the mean value of the B.M.R.S for the 20 patients was +47 0, at the

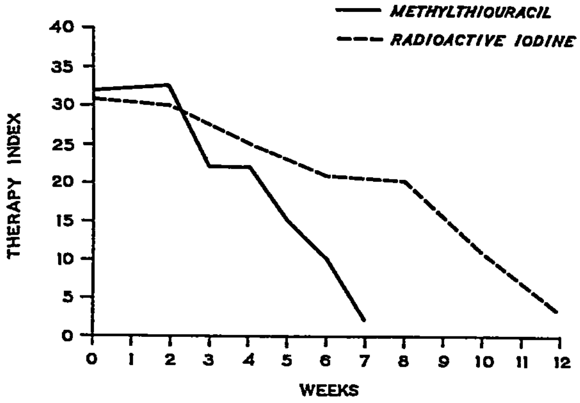

Fig 3—Rate of change of the therapy index produced by methylthiouracil and by radioactive iodine

conclusion or rather at 0 55 week before " cure " the mean value was —3 9 with a standard deviation of 9 2 A normal group of individuals would be expected to have a B.M R. whose mean value is 0 and standard deviation 7 5 approximately Since the mean value of —3 9 is not significantly different from 0 (0 5 < P < 0 10), the 20 patients had attained the euthyroid state as assessed by the B.M R. criterion. At the beginning of treatment using potassium perchlorate the mean of the initial readings of B M.R.S for the 20 patients was +35 7, at the conclusion or rather at 0 35 week before " cure " the mean value was 0 0, with a standard deviation of 10 6 Thus once again the

TABLE IV—TIMES TAKEN TO EFFECT " CURE " IN PATIENTS WHO RELAPSED AFTER TREATMENT SERIES 2

Patient no	Time to effect ' cure (weeks)		Difference (weeks)	Patient no	Time to effect ' cure " (weeks)		Difference (weeks)
	Methylthiouracil initial therapy	Potassium perchlorate retreatment			Potassium perchlorate initial therapy	Methylthiouracil retreatment	
21	9	12	−3	7	18	10	+8
22	10	10	0	9	14	7	+7
23	9	22	−13	10	11	9	+2
24	11	9	+2	11	7	4	+3
25	15	22	−7	13	13	14	−1
26	10	12	−2	14	9	4	+5
27	7	16	−9				
33	6	6	0				
Mean time to " cure	9·6	13 6	−4·0		12·0	8·0	−4·0

estimation of the B M R confirmed that patients had attained the euthyroid state

Series 2 ("Cross-over" Observations)

In series 2 the time taken to effect "cure" in 8 subjects who initially received methylthiouracil and who, after recurrence of the disease were given potassium perchlorate, are shown in table IV "Cure" was also confirmed by B M R estimations in this group of subjects

A t-test shows that the difference of 4 weeks is not significantly different from zero ($t=-2{\cdot}18$, $0{\cdot}05<P<0{\cdot}10$) It should, however, be noted that the difference found—i e, that potassium perchlorate took 4 weeks longer than methylthiouracil for "cure" to be obtained in the same patients—is similar to the difference found in series 1 in which different patients were given the two drugs In 6 subjects who had received potassium perchlorate and who were given methylthiouracil after recurrence of the disease, the times to "cure", confirmed by B M R s, are also shown in table IV A t-test shows that in this group of subjects the difference of 4 weeks is significantly different from zero ($t=-2{\cdot}93$, $P<0{\cdot}05$) Again the slower rate of control by perchlorate is similar to that obtained between the two groups of 20 patients in series 1

The findings in these two "cross-over" tests show that it does not matter which drug is given first It is valid therefore to consider both "cross-over" tests together and to conclude that in this group of 14 subjects potassium perchlorate in the doses used took 4 weeks longer than methylthiouracil to control the disease These observations confirm the results of series 1 and provide evidence that the method of assessment is reproducible They also show that the "cross-over" type of control is unnecessary and that no fallacy has arisen from the method of using alternate cases for the two drugs

Comparison of the Response to Antithyroid Drugs and Radioactive Iodine

The therapy index can be used to compare the response to antithyroid drugs with other forms of treatment—e g, radioactive iodine Fig 3 illustrates the rate of response in one patient treated with 7 mC of radioactive iodine compared with the patient shown in fig 1A treated with methylthiouracil We are now using the method to study the therapeutic response of a group of patients who have been treated with radioactive iodine

Discussion

There are many advantages in being able to follow quantitatively the degree of improvement which results from therapeutic procedures, and the purely clinical method we describe here makes it possible to obtain more consistent estimates of a patient's progress than when conventional methods are used Thus when it is necessary for the same patient to be seen from time to time by different clinicians, our system of scoring tends to eliminate personal bias in the interpretation of the observations The proforma also acts as an aide-memoire enabling facts to be recorded and analysed quickly It should be stressed that in systems of this type it is necessary to use a standard method of history-taking and to adopt rigid criteria for the recognition of physical signs Used as a method of scientific investigation our scheme enables statistical methods to be applied to the results of treatment In the present study for example, it has enabled us to show that the usual therapeutic response to antithyroid drugs is linear with time It has also brought out the absence of any relationship between the initial severity of the disease and the rate of therapeutic response

We feel, however, that the main value of this method of assessment is to provide a more accurate method of comparing the therapeutic effectiveness of different antithyroid compounds There are comparatively few ways in which this can be done In animals, methods depending on their goitrogenic action have been devised using either the immature rate (Astwood et al 1945) or the chick (VanderLaan and Bissell 1946) In man, Stanley and Astwood (1947) have shown that the property which some antithyroid drugs possess of inhibiting the uptake of radioactive iodine can be utilised to give a measure of their relative potencies Though this technique has the great merit that the comparison is made in the human subject, it is known that the results are not necessarily applicable to a patient suffering from thyrotoxicosis Moreover, it is valid only when applied to drugs which act at the same point on the chain of thyroid-hormone synthesis and so cannot be used to compare the activity of drugs such as potassium perchlorate with the thiouracils and imidazoles since the former act on the iodide-trapping mechanism whereas the latter affect the conversion of iodide to organically bound iodine

Drugs should, if possible, be assayed on patients suffering from the disease for which they are to be used, so that the pharmacological mechanisms underlying their effect becomes relatively unimportant For this reason we believe that the ratio between the effectiveness of methylthiouracil and potassium perchlorate in the doses we chose is the most accurate figure so far recorded It is of great interest, and provides strong confirmatory evidence of the validity of our method, that an almost identical difference in activity was shown in two separate experiments of different design In both series of cases the conclusions were confirmed by estimation of B M R In the second series each patient acted as her own control and the method used is an application to man of the "cross-over" tests used in animals by experimental pharmacologists So far as we know this is the first example of the use of this particular technique in human pharmacological investigations There are, of course, few conditions in which it is permissible to stop the administration of an effective drug and to allow the patient to relapse before using a second form of treatment These observations also showed that the order of administration of the two antithyroid drugs did not affect the final result

We believe that this scoring system of assessing therapeutic response in thyrotoxicosis is widely applicable We have described in this paper how it can be used to compare the activities of two antithyroid drugs The doses we used were those which we were using when the tests were begun, and the results indicate that, weight for weight, methylthiouracil is more potent than potassium perchlorate Further observations, which will be the subject of a separate communication, show that this is a question of dosage, and that in higher doses potassium perchlorate is an equally effective form of treatment

Summary

A clinical method of comparing the relative effectiveness of therapeutic procedures in thyrotoxicosis is described It is based on the allocation of numerical values to those features of thyrotoxicosis which can be reversed by treatment The sum of these values is called the therapy index and can be used to assess the progress of an individual case We illustrate its use in the comparison of two antithyroid drugs Thus therapy indices were recorded weekly in two groups of 20 cases, one group receiving methyl-

thiouracil and the other potassium perchlorate The antithyroid activity of both drugs was assessed by the time taken for the index to fall within the range 0 to 5 Estimations of the basal metabolic-rate confirmed that at this level patients were euthyroid The time taken to reach the euthyroid state was independent of the initial severity of the disease In 33 of 40 patients the rate of therapeutic response bore a linear relationship to time Methylthiouracil in doses of 600 mg a day for three weeks followed by doses of 300 mg a day was shown to be a more effective antithyroid drug than potassium perchlorate in doses of 600 mg a day A " cross-over " test carried out on 14 patients, who had relapsed after a first course of treatment, confirmed this conclusion

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A COMPARISON OF
POTASSIUM PERCHLORATE, METHYLTHIOURACIL, AND CARBIMAZOLE IN THE TREATMENT OF THYROTOXICOSIS

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At some time during the course of their disease the majority of patients with thyrotoxicosis receive an antithyroid drug It is probable that these substances provide the most satisfactory form of treatment for most young patients and the speed and certainty of their action often make their immediate administration necessary even when it has been decided subsequently to use an alternative form of treatment. It is obviously of importance to know which is the most effective and the safest member of the group The ideal antithyroid drug should be rapid in its action and should produce no adverse side-effects In this country the two most commonly used drugs are methylthiouracil and carbimazole In other countries propylthiouracil and methimazole are popular All, however, occasionally produce toxic effects, of which agranulocytosis is the most serious since it may prove fatal The most common adverse reaction is the drug rash, but nausea, drug fever, aplastic anæmia, thrombocytopenia, conjunctivitis, and lymph-gland enlargement have all been reported

Methylthiouracil was first introduced in 1944 and was for long the standard antithyroid substance in use in this country Carbimazole received favourable reports in 1953 from Doniach and from Poate. It was said to produce fewer side-effects than methylthiouracil although its action was slower Its use has tended to increase especially since evidence that it is less toxic was produced by Greene and Morgan (1956) and by Burrell et al (1956) It is said to be ten times as active as methylthiouracil and is usually given in one-tenth of the dose The *British Pharmacopœia* recommends that the controlling dose of methylthiouracil should be from 0 2 to 0 6 g daily and of carbimazole from 30 to 60 mg daily

Potassium perchlorate is a rival and more recent antithyroid drug with a different type of action Unlike the thiouracils and imidazoles which prevent the iodination of tyrosine, it acts by inhibiting the iodide-trapping mechanism of the thyroid gland As a simple inorganic compound it would seem a priori to be less likely to produce sensitisation effects than the organic antithyroid substances, and in particular to be less likely to damage the hæmopoietic system It was first shown to be a suitable substance for clinical use by Godley and Stanbury (1954) This was confirmed in a much larger series of cases by Morgans and Trotter (1954) who found that the rate of response produced by 400 mg daily was less than that produced by methylthiouracil in a dose of 200 mg daily

Shortly after their report was published we decided to assess the relative merits of potassium perchlorate, methylthiouracil, and carbimazole We shall present our conclusions based on a study of more than 450 patients It soon, however, became evident that while the comparative incidence of the side-effects of these substances would be revealed by this investigation a comparison of their relative efficacy presented a more difficult problem For this reason we devised a clinical method of comparing antithyroid drugs based on the allocation of points to those features of thyrotoxicosis which are reversible by therapeutic measures This enabled us to derive a " therapy index " which could be followed from week to week and the time taken for it to reach and remain at a value of 5 or lower could be used as a measure of the effectiveness of the form of treatment We have already recorded in illustration of our method a comparison of the effect of 600 mg daily of potassium perchlorate with that of methylthiouracil in doses of 600 mg daily for two weeks followed by 300 mg daily Using these dosage schemes methylthiouracil was more effective (Crooks et al 1960) It seemed to us probable that this result depended on the relative doses used and a further series of cases has been studied using 1000 mg of potassium perchlorate daily Since our clinical experience had led us to doubt the statement that carbimazole is, weight for weight, ten times as active as methylthiouracil we also compared these two substances

Potassium perchlorate proved to be both effective and relatively free from side-effects and we now use it routinely We have, therefore, studied more closely some of its alleged disadvantages notably the tendency for its activity to be affected by variations in the dietary intake of iodine and its liability when used before operation to produce an unduly vascular gland We also report the results of its use in pregnant patients with thyrotoxicosis

Material and Methods

We have studied two further groups of 20 cases in addition to the two already reported (Crooks et al 1960)

All the patients had diffuse goitres and exophthalmos and thus were examples of classical Graves's disease To one group carbimazole was given in doses of 20 mg three times a day for two weeks followed by 10 mg three times a day (i e , one-tenth of the dose of methylthiouracil which was used in our previous series) Potassium perchlorate was given to the other group in a dose of 200 mg 5 times a day The dietary intake of iodide was not restricted.

The method of comparison was that used in the earlier series except that estimations of basal metabolic-rate (B M R.) were made only at the end of the investigation to confirm that the patients were euthyroid

TABLE I—DISTRIBUTION OF PATIENTS IN SERIES 3 RECEIVING CARBIMAZOLE AND POTASSIUM PERCHLORATE (1000 MG DAILY) SHOWING TIME TAKEN TO EFFECT "CURE"

Time to effect "cure" (weeks)	Carbimazole (no of patients)	Potassium perchlorate (1000 mg daily) (no of patients)
3–4		
5–6		8
7–8	7	3
9–10	2	4
11–12	4	1
13–14	3	2
15–16		1
17–18	2	
19–20		1
21–22	2	
Total	20	20
Mean time to "cure"	12·3 weeks	9·4 weeks

The study of the comparative toxic effects of these substances is based on observations made on 486 patients seen and treated by us in our wards or clinic. After reference to their general practitioner they continued to attend hospital from time to time so that the occurrence of toxic effects could be accurately recorded.

Results

"*Therapy Indices*"

The times taken to effect "cure" for both drugs are shown in table I. The mean time to "cure" of the 20 patients on carbimazole was 12·3 weeks and the corresponding figure for potassium perchlorate was 9·4 weeks.

Table II gives the mean times to "cure" of the groups treated with methylthiouracil, carbimazole, and potassium perchlorate in doses of both 600 mg. and 1000 mg. daily.

For the purpose of statistical analysis the drugs have been represented by the letters A, B, C, and D as shown in the table. An analysis of variance on the 80 patients studied shows that there are significant differences between the mean values for A, B, C, and D. In particular A is significantly different from B and C ($P < 0.05$), D is significantly different from B and C ($P < 0.05$), and there was no significant difference between A and D. A further analysis of variance was carried out on the 60 patients remaining after the exclusion of those who had been given methylthiouracil. It was found that there was a significant difference between B and D ($P < 0.05$), a significant difference between C and D ($P < 0.05$), and no significant difference between B and C.

TABLE II—MEAN TIMES TO EFFECT "CURE" FOR METHYLTHIOURACIL, POTASSIUM PERCHLORATE, AND CARBIMAZONE

Drug	Time to effect "cure" (weeks)
A Methylthiouracil	9·1
B Potassium perchlorate (600 mg daily)	13·1
C Carbimazole	12·3
D Potassium perchlorate (1000 mg daily)	9·4

These results can be summarised as follows: methylthiouracil in doses of 600 mg. daily for 2 weeks followed by 300 mg. daily and potassium perchlorate (1000 mg. daily) were equally effective as measured by the time taken to effect "cure", while both were more effective than carbimazole in one-tenth of the dose of methylthiouracil or potassium perchlorate (600 mg. daily).

Effect of Variations in the Intake of Iodine on Potassium Perchlorate Therapy

Potassium perchlorate affects the iodide-trapping mechanism of the thyroid and it is known that the goitrogenic action of substances with this action can be overcome if sufficient iodide is given (Franklin et al. 1944). In our earlier series we advised patients given potassium perchlorate 600 mg. daily, to restrict their iodine intake by excluding fish from the diet, by using uniodised salt, and by avoiding medicines.

Diet histories from 8 patients and urinary assays from 20 patients revealed a great variation in the degree to which iodide restriction had been achieved. The therapeutic responses to potassium perchlorate of patients with relatively high and low intakes were statistically analysed and no difference was found. In our later observations therefore we have urged no dietetic restrictions and have merely advised patients to avoid certain cough medicines which contain iodide in relatively large quantities.

Preoperative Use of Potassium Perchlorate

It is generally agreed that antithyroid drugs should be used to prepare a thyrotoxic patient for partial thyroidectomy. The usual method is to bring the disease under control with one of the organic antithyroid drugs and then to give iodide for 10–14 days before operation. It is said that this renders the gland less vascular and diminishes the likelihood of postoperative thyroid crises.

Godley and Stanbury (1954) prepared 13 patients for operation with potassium perchlorate and stated that the consensus of opinion of the operating surgeons was that a few of the glands were more vascular than those of patients prepared with propylthiouracil and iodine. 2 patients who before operation received iodide in addition to perchlorate escaped from control. For this reason Morgans and Trotter (1954) did not use perchlorate in those patients who were likely to require partial thyroidectomy.

We have prepared 20 patients for operation with potassium perchlorate alone. 18 of these patients had small nodular glands and the surgeon did not find more technical difficulty due to increased vascularity of the gland than after conventional preparation.

Opinions as to the degree of vascularity must of necessity be highly subjective. It may well be that contradictory views on the effects of the antithyroid drugs on vascularity are due to variation in the selection of cases and to the lack of an investigation designed so as to eliminate the effects both of biological variation and of bias on the part of the surgeon. The blocking effect of potassium perchlorate on thyroid hormone synthesis continues for some time after the drug has been withdrawn and administration can cease at the time of operation.

Use of Potassium Perchlorate During Pregnancy

Opinion is almost unanimous that the most appropriate form of therapy for women who develop thyrotoxicosis during pregnancy is the administration of an antithyroid drug. Goitre and hypothyroidism have been reported in the infants of mothers who have received these substances but it is rare, and when it occurs the dosage has almost always been unduly high (Macgregor and Goodwin 1953). We have treated 12 pregnant thyrotoxic patients with potassium perchlorate and in each have achieved satisfactory control of the disease. One of the infants had a very slight enlargement of the thyroid gland which disappeared within 6 weeks. The remainder showed no abnormality of any kind. We report these results to show that the different mode of action of potassium perchlorate and its special physical properties do not render it more liable to affect the fœtal thyroid than the antithyroid substances in more common use.

Toxic Effects of Antithyroid Drugs

We have treated 486 patients with either methylthiouracil, carbimazole, or potassium perchlorate for sufficiently long to be able to assess their relative tendency to give rise to toxic side effects. Table III shows our results. No statistically significant difference was found

TABLE III—TOXIC EFFECTS

Toxic effect	Methyl-thiouracil (600 mg daily 2 wks, then 300 mg daily)	Carbimazole (60 mg daily 2 wks, then 30 mg daily)	Potassium perchlorate	
			600 mg * or 1000 mg	1500 mg † or 2000 mg
No of cases	151	85	200	50
Skin rashes	5	4	1	5
Nausea		1	3	2
Drug fever	2			
Agranulocytosis	2	2		1
Thrombocytopenia	1			

* 35 patients † 10 patients

between the liability of the organic substances to produce sensitisation reactions such as skin rashes or blood dyscrasias Potassium perchlorate, on the other hand, in doses of 1000 mg a day or under was less likely than the organic antithyroid compounds to produce adverse effects of this type Higher doses of potassium perchlorate produced reactions as frequently as the organic compounds

The rashes produced by potassium perchlorate were maculopapular and were confined to the extremities except in 1 patient in whom the rash was generalised. This patient had an associated pyrexia and marked desquamation followed the disappearance of the eruption. In 3 of the 6 cases the rash subsided although the administration of the drug was continued.

The patient with agranulocytosis was a young woman receiving 1500 mg of potassium perchlorate a day During the third week of treatment she developed a sore throat, pyrexia, and generalised muscular pain. Blood examination showed a total polymorphonuclear leucocyte count of 750 per c.mm. The peripheral blood was otherwise normal and the bone-marrow showed no evidence of a maturation defect of the white-cell series. Administration of the drug was stopped and the leucocyte count rose rapidly to normal levels The patient had received no other drugs which might have caused leucopenia.

The rashes produced by the organic antithyroid compounds were all maculopapular This is a type of eruption which is well known to occur in those who become sensitised to this series of compounds Urticaria which has also been reported was not observed in this series

4 patients complained of nausea while taking potassium perchlorate. 3 of them were able to continue taking the drug when an antacid mixture was given along with it and the nausea disappeared within a week. The fourth refused further treatment.

Discussion

The " therapy index " has been used to assess the rate of improvement in four different groups of patients suffering from classical Graves' disease One group received carbimazole, one methylthiouracil, and the other groups potassium perchlorate in two different doses From these investigations we are able to draw two conclusions First, carbimazole is less effective than methylthiouracil when given in one-tenth of the dose Secondly, potassium perchlorate is more effective in high than in low dosage

The very extensive literature on the antithyroid drugs is fully reviewed by McGavack (1951), Werner (1955), and Crooks (1957), and it is clear that the four drugs most widely used at present are methylthiouracil, propylthiouracil, methimazole, and carbimazole All are effective and relatively safe The particular substance used by any given physician seems to be determined by two factors In the first place it is clear that the country of origin is important since methylthiouracil and carbimazole were both first synthesised and marketed in Europe whereas propylthiouracil and methimazole were originally American products The second factor of importance is the relative conservatism of the individual clinician. Most physicians see no reason to try a new remedy if the existing one is satisfactory although some are impressed by new substances even if their advantages are marginal Moreover, any clinician tends to be overimpressed by an example of a patient under his care who shows a serious side-effect even though the statistical hazards of this occurrence can be shown to be small Against this background of national and individual prejudice there is almost no statement which has not been made about the relative effectiveness, speed of action, and toxicity of these drugs

We have found no published observations on the relative dosage of antithyroid drugs which cannot be explained on the view that the response of a patient to an antithyroid drug is a function of the dose At a certain critical level a dose is reached at which synthesis of the thyroid hormone is completely blocked Inspection of curves showing the effect of different doses of methylthiouracil on the uptake of radioactive iodine by the gland, as reported, for example, by Goodwin et al (1949), illustrate this phenomenon.

The first problem in dealing with the dose of an antithyroid drug is to discover the least dose which in the majority of patients will effectively block secretion of the thyroid hormone during each 24 hours This is probably of the order of 450 mg for methylthiouracil, 60 mg for carbimazole, and 1000 mg for potassium perchlorate The question then arises of the relative liability of these drugs to produce toxic side-effects In spite of their importance we know relatively little about sensitisation reactions to drugs It is not possible, for example, to say with certainty whether they are dependent on dose With some drugs (e g , amidopyrine) a single dose may produce a reaction in a sensitised patient With others, such as chloramphenicol or the sulphonamides, there seems to be a tendency for reactions to be related to total dosage In the case of the antithyroid substances the balance of evidence seems to suggest that they belong to the latter type (Lehr 1948) Certainly our own results show that potassium perchlorate produces more reactions in high than in low dosage It seems therefore to us that it is unjustifiable to group together series of cases collected from the literature without allowing for this factor of dosage and without applying statistical tests of significance to all the results reported The two published comparisons of carbimazole and methylthiouracil (Burrell et al 1956, Greene and Morgan 1956) are thus rendered inconclusive

Our tentative conclusions are these There is no convincing evidence that any of the organic antithyroid drugs is significantly more toxic than any other when it is given in therapeutically equivalent dosage Our experience suggests that potassium perchlorate is less liable to give rise to skin rashes or blood dyscrasias in doses which act as quickly as the conventional therapeutic doses of methylthiouracil and carbimazole

Potassium perchlorate thus appears to us to be the antithyroid drug of choice A few observers other than Godley and Stanbury (1954) and Morgans and Trotter (1954) have used it and found it satisfactory Thus Kleinsorg and Kruskemper (1957) treated 47 cases with doses of 1 6 to 2 0 g a day, 2 patients developed a rash Buttaro and Brunori (1955) reported 25 patients successfully treated with doses of 600 mg a day and 1 developed a skin rash Observations in our series showed that it is unnecessary to restrict the dietetic intake of iodine during the administration of potassium perchlorate In our experience this drug can be satisfactorily used for preoperative preparation when the gland is small and nodular Whether or not it can be used in this way when the gland is large requires further investigation

Sensitisation to potassium perchlorate can occur The usual manifestation is a rash which usually subsides quickly even if administration is continued It is much more likely to develop when the dosage is high Our single case of agranulocytosis occurred in a patient receiving large doses of the drug but if the use of potassium perchlorate increases we should not be surprised to learn that this serious condition may be associated with lower doses or that the bone-marrow may be affected in other ways The balance of present evidence, however, is in favour of its very low toxicity It has the additional merit of being very cheap and it is of some interest that the only proprietary preparation of potassium perchlorate was for many years in category 5 of the List of Proprietary Medicines Classified by the Joint Committee on Prescribing which is published jointly by the Ministry of Health and the Department of Health for Scotland

Summary

A clinical method of assessing the rate of improvement of groups of patients suffering from thyrotoxicosis has been applied to four series of cases receiving respectively methylthiouracil, carbimazole, and potassium perchlorate in two different doses Carbimazole was less effective than methylthiouracil when given in one-tenth of the, dose Potassium perchlorate in high dosage was as effective as methylthiouracil and more effective than carbimazole and smaller doses of perchlorate

Four larger series of patients receiving these drugs were studied to ascertain the incidence of toxic side-effects Potassium perchlorate in a daily dose of 600–1000 mg produced fewer side-effects than when it was given in daily doses of 1 5–2 0 g The lower dosage range also gave rise to fewer side-effects than either methylthiouracil or carbimazole in therapeutically equivalent doses No statistical difference in the incidence of sensitisation reactions was found between the latter two substances

Potassium perchlorate in high doses is liable to produce skin rashes, and in 1 of our cases agranulocytosis developed

It is not necessary to restrict the dietary intake of iodine during perchlorate administration It can be used to prepare patients for thyroidectomy when the gland is small and nodular and can also be used during pregnancy Potassium perchlorate, 1000 mg daily in divided doses, is the antithyroid drug of choice in the medical treatment of thyrotoxicosis

We wish to thank Dr R A Robb, Mitchell lecturer in statistics, University of Glasgow, for help with the statistical aspects of this work, and Mr D H Clark, F R C S, who carried out the thyroidectomies to which we refer

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THE INCREASE IN DIFFUSING CAPACIT OF THE LUNGS ON EXERCISE

AN EXPERIMENTAL AND CLINICAL STUDY

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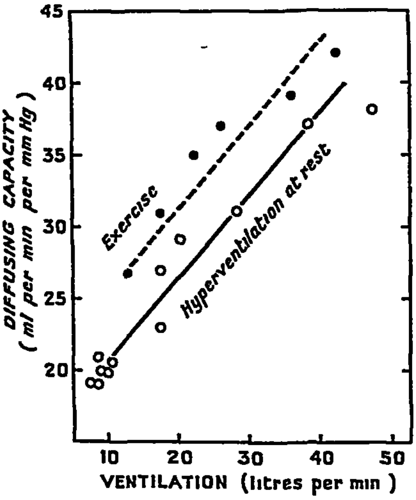
When oxygen is taken up from the alveoli of the lun it has to penetrate the mechanical barrier of the tiss elements and fluids separating it from the molecules hæmoglobin in the red cells, the process is one of simp physical diffusion Methods of measuring the perme bility of this barrier to gases have been elaborated whic permit an estimate of the so-called *diffusing capacity* the lungs The simplest of these uses carbon monox as the test gas, and measures its rate of absorption in th steady state (Bates, Boucot, and Dormer 1955) Th measured rate of uptake of this gas in low concentratio in an inspired gas mixture is divided by its mean alveol concentration during the test (expressed as parti pressure) to give a result in ml per min per mm Hg. On physical principles, it may be assumed that the diffusing capacity thus measured is proportional to the area of the diffusing surface and varies inversely with its thickness Normal results vary between 15 and 25 ml per min per mm Hg at rest and from 25 to 40 ml during exercise Experience in the past few years in many centres has shown how valuable measurements of diffusing capacity are clinically, moreover, many facts of physiological interest and importance have been revealed by them Among the latter is the observation, repeatedly confirmed, that the diffusing capacity is greatly increased during exercise The object of this communication is to report some investigations which throw light on the way in which this change is brought about

Investigations and Conclusions

In an experimental assessment of the steady-state method of measuring pulmonary diffusing capacity using carbon monoxide (MacNamara, Prime, and Sinclair 1959) we drew attention to the fact that the results obtained were significantly dependent on the minute-volume of respiration during the test This finding made us wonder whether the apparent increase in diffusing capacity on exercise was due entirely to the effects of hyperventilation We therefore measured the diffusing capacity in four healthy subjects at rest during voluntary hyperventilation at various rates We found that the diffusing capacity rose steadily with increasing ventilation, showing no definite tendency to a maximum value within the range of voluntary hyperventilation which it was possible to maintain for the time required for the test These results were compared with values of diffusing capacity in the same subjects, measured at various rates of exercise, by plotting both sets of values on a graph relating them to pulmonary ventilation Contrary to our expectation, we found that the curves plotted from the exercise values did not coincide with those for voluntary hyperventilation but lay above them A typical comparison in one subject is shown in the figure This discovery has since been confirmed by results published by two groups working independently in America (Ross, Frayser, and Hickham 1958, and Turino, Brandfonbrener, and Fishman 1959)

We concluded that some factor other than hyperventilation contributed to the increase occurring during exercise and that this was most likely to be the consequence of the increased pulmonary blood-flow Before proceeding further we excluded, by suitable experiments, the possibility that our findings were the result of sampling errors or changes in mean lung volumes (see appendix) We then considered how best to assess the effects of increasing pulmonary blood-flow and decided as a first step to measure diffusing capacity in a number of patients with congenital heart-disease without pulmonary hypertension, in whom pulmonary blood-flow had been measured by cardiac catheterisation and found to be above normal The data collected from these patients are set out in the table. We found that in all of them diffusing capacity was above normal at rest, but was not increased beyond normal on moderate exercise, in other words, the range of change observed between rest and exercise was not so great as in normal subjects, although the minute-volume of respiration increased in a normal manner



Plot of values of D_L during hyperventilation at rest (o) and during periods of exercise of differing severity (●) in one subject

No mention has yet been made of similar findings by other workers Ross et al were unable to demonstrate any increase in diffusing capacity at rest when cardiac output was increased as much as twofold by administration of atropine or noradrenaline to normal subjects, whilst Turino et al failed to find results below normal in subjects with a low cardiac output due to mitral stenosis

PULMONARY DIFFUSING CAPACITY FOR CARBON MONOXIDE (D_L) MEASURED BY THE STEADY-STATE TECHNIQUE AT REST AND DURING EXERCISE IN 10 PATIENTS SUFFERING FROM AURICULAR SEPTAL DEFECT WITH HIGH PULMONARY BLOOD-FLOW (CO) BUT NO INCREASE IN PULMONARY VASCULAR RESISTANCE

Expected values for D_L at rest are shown in parentheses, they are derived from values obtained in healthy subjects of the same height and weight

Patient	Age and sex	Height (in)	Weight (lb)	Pulmonary ventilation (litres per min.)		D_L (ml. per min per mm. Hg		CO (l per min.) at rest
				Rest	Exercise	Rest	Exercise	
1	14 F			11 2	27 7	25 ( )	29	22
2	15 M	60	99	7 7	22·9	33 (15)	36	15
3	16 M	62	112	9·4	19 6	29 (17)	33	8
4	17 F	68	118	7 1	18 9	28 (20)	33	19
5	18 M	64	113	7 8	20 8	37 (19)	46	14
6	36 M	66	122	6 3	27 5	24 (20)	39	13
7	36 F			10·0	29·0	27 ( )	40	23
8	45 F	64	126	14·0		32 (20)		30
9	46 M	70	140	12·0	28 3	31 (23)	34	22
10	46 M	66	136	9 8	25·6	33 (22)	40	15

The findings described suggest very strongly that the increase in diffusing capacity accompanying exercise is in large part mediated by the hyperventilation that exercise induces Voluntary hyperventilation probably increases the area of the capillary wall separating blood and gas, either by actually distending the pulmonary capillaries with blood or by causing alveoli which are more or less functionless during quiet breathing to become ventilated and perfused The high diffusing capacity observed in the patients suffering from atrial septal defect is likewise due probably to an increase in pulmonary alveolar-capillary blood volume with a consequent increase in area of the interface between blood and gas The most likely reason for the failure to detect any change in diffusing capacity when pulmonary blood-flow is increased by drugs (Ross et al 1958) is that these substances had no effect on pulmonary capillary blood volume, pulmonary blood-flow per se would be expected to have no effect on the rate of carbon-monoxide uptake from the alveolar gas

The possibility should be mentioned that hyperventilation in the absence of exercise may produce values for diffusing capacity which are lower than they should be because a high alveolar oxygen tension depresses the rate of uptake of carbon monoxide by hæmoglobin During hyperventilation at rest alveolar oxygen tension may rise as high as 125 mm Hg which is about 30 mm. Hg higher than that found during heavy exercise Calculation from data published by McNeil, Rankin, and Foster (1958) shows that this difference could depress the pulmonary diffusing capacity by about 2 ml per min per mm Hg during voluntary hyperventilation This estimate represents the highest possible effect of the difference in alveolar oxygen tension in these two states, in most of our experiments exercise was not very severe and was not probably accompanied by a fall of alveolar oxygen tension below about 100 mm Hg Thus it is possible that about half the observed difference in level between the results on exercise and those during voluntary hyperventilation may be due to this effect.

We therefore conclude that the observed increase in pulmonary diffusing capacity during exercise is due primarily to an increase in the area of capillary wall exposed to alveolar gas This is mediated partly by the hyperventilation itself and partly by the increased cardiac output in exercise.

Summary

In patients suffering from atrial septal defect with high pulmonary blood-flow but without pulmonary hypertension the pulmonary diffusing capacity is considerably higher than normal, exercise increases it relatively less than in normal subjects This indicates that the area of blood-gas interface is the important factor underlying the increase in diffusing capacity which occurs in normal subjects during exercise and during voluntary hyperventilation

Appendix

Pulmonary diffusing capacity (D_L) was measured in these experiments by a method similar to that of Bates et al (1955) fully described by MacNamara et al (1959)

1 We excluded errors of sampling as a cause of the increase in D_L observed during voluntary hyperventilation by taking our alveolar samples simultaneously at two points in expiration separated by 450 ml of expired gas When tidal volumes were of the order of 1 litre and over, little difference was found between these samples

2 That the observed change was not solely due to large swings in intrathoracic pressure we confirmed by constricting the airway of the apparatus while the subject maintained a normal rate and depth of breathing This procedure did not alter the value of D_L, although respiratory pressure swings of 40–50 cm of water were induced which are of the same order as those encountered during vigorous hyperventilation with a free airway

3 We carried out the tests with the subjects breathing with their chests voluntarily held above the resting respiratory position so that the volume of gas contained by the lungs at the end of each breath was up to 21 above normal This manœuvre had no effect on the diffusing capacity, confirming Marshall's previous findings (Marshall 1958)

4 Finally we arranged our apparatus so that the subjects hyperventilated against a constant positive pressure of about 15 cm of water, the object of this manœuvre was to drive blood out of the lungs and thus, on our hypothesis outlined above, to prevent or limit the expected increase in D_L This experiment failed to achieve its object, probably because the pressure used was too low, pressures higher than this could not be tolerated long enough for the tests

Our thanks are due to Dr J G Scadding and our laboratory staff who have helped us considerably in the production of this work

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TRANSTHORACIC VAGOTOMY FOR STOMAL ULCERATION

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STOMAL ulceration following gastric resection is not common, while stomal ulceration following gastro-enterostomy is seen only as an occasional legacy of the past Both these groups of cases can be treated by gastric resection with excision of the ulcer, which may or may not include an abdominal vagotomy Abdominal vagotomy alone, as a planned procedure, may prove very difficult, and, whether it be difficult or easy, the surgeon may be tempted to change his plan and resect an ulcer mass that would be better left alone Transthoracic vagotomy, as the sole procedure, is an alternative which offers certain definite advantages such as technical ease, very low morbidity and mortality rates, and freedom from the sequelæ of extensive excision of the stomach We describe here our results with this procedure

Last April we reviewed all the cases of stomal ulceration seen on the professorial unit at the Liverpool Royal Infirmary between December, 1952, and mid-1957 and treated solely by transthoracic vagotomy All but a few were personally questioned and examined 2 remain untraced (a common experience in a seaport town), leaving for assessment 23 (17 males, 6 females), the youngest of whom was 28 and the oldest 73 at the time of operation

TABLE I—RESULTS OF TRANSTHORACIC VAGOTOMY FOR STOMAL ULCERATION

Previous operation	No of cases	Failures
1 Gastro-enterostomy	4	0
2 Gastric resection		
Polya	5	0
Steinberg [1]	2	1
Roux-Y	4	1
Billroth I (including modified [2] Billroth I)	5	2
Moroney [3]	3	2

1 Double-lumen gastrojejunal anastomosis of the "pantaloon" type
2 End-to-side gastroduodenal anastomosis with wide stoma
3 Colonic implant between stomach and duodenum with reversed peristalsis

Barium-meal examination had provided definite evidence of ulceration in 12 cases and suggestive evidence in 4 In the remaining 7 there were strong clinical grounds (severe epigastric pain, vomiting and/or bleeding) for the diagnosis of stomal ulceration Gastroscopy was carried out in some cases, but gave little help Fractional test-meal was performed in most cases, provided supportive evidence in 11 where high or average acid levels were found Negative findings in test meals after gastric operations are notoriously unhelpful We have not used the insulin-provoked test meal for gastric acidity after vagotomy Today the twelve-hour overnight secretion would ordinarily be estimated, but this was not done routinely in our series

No deaths had resulted from the operation nor any major complications While in hospital some patients had had segmental left-lower-lobe collapse with a small effusion, and for a few months after operation a minority complained of wound pain

Results

The results are summarised in table I

Gastroenterostomy group (4 patients)—The stomal ulceration had developed fourteen to twenty-five years after gastroenterostomy Vagotomy relieved all four patients of their ulcer symptoms and they were well at the time of follow-up

Gastric-resection group (19 patients)—The majority had previously had more than one operation In 13 all symptoms were removed by thoracic vagotomy and 11 of these were well at the time of follow-up The other 2 had died from unrelated causes

The first had developed stomal ulceration after a Steinberg gastrectomy and was relieved by vagotomy, but he died six years later from carcinoma of the bladder The second, whose stomal ulcer followed a Billroth I gastrectomy for gastric ulcer, was also relieved by vagotomy but died of cirrhosis of the liver nine months after the operation

Of the remaining 6 (unrelieved) cases, no fewer than 4 proved to have been badly selected 1 patient, who had had a Roux-Y gastrectomy, was a chronic alcoholic and was afterwards admitted to a mental home The other 3, who had complained of epigastric pain and vomiting, were found at subsequent laparotomy to have no evidence of stomal ulcer, active or healed Their histories are

CASE A (*Steinberg gastrectomy*)—1951 gastropexy elsewhere for partial gastric volvulus 1952 Steinberg gastrectomy for duodenal ulcer and hiatus hernia 1953 transthoracic vagotomy (confirmed histologically) failed to relieve persistent epigastric pain 1958 no ulcer found at laparotomy Converted to "Moroney" Since then the attacks of epigastric pain have been less frequent, they seem to have been due to intestinal hurry

CASE B (*modified Billroth I*)—1952 pylorectomy and vagotomy for duodenal ulcer, performed elsewhere 1953 modified Billroth I for persistent duodenal ulcer 1957 transthoracic vagotomy On histological examination, amputation neuromata found Symptoms unrelieved Roux-Y conversion carried out as a last resort but without improvement

CASE C (*Moroney*)—1926 gastroenterostomy *1916–47* Polya gastrectomy for recurrent ulceration Severe nutritional deficiencies followed (anæmia, pellagra, riboflavin deficiency) probably as a result of extreme intestinal hurry (barium was demonstrated in the cæcum an hour after ingestion). 1952 Moroney conversion for intestinal hurry. 1953 transthoracic vagotomy for suspected stomal ulcer. 1956 Roux-Y conversion after excision of colonic implant (no ulcer found). Pain, vomiting, and nutritional deficiencies persist, albeit to a lesser extent. A recent barium meal was negative. Fasting test-meal showed achlorhydria.

In the 2 other patients stomal ulceration continued despite transthoracic vagotomy.

CASE D (*modified Billroth I*).—1953 Modified Billroth I, with abdominal vagotomy for duodenal ulcer. 1955 transthoracic vagotomy for a stomal ulcer (bilateral vagal-nerve section was confirmed on histological examination). 1957 insulin test-meal at blood-sugar 35 mg. per 100 ml. produced 100 clinical units of total acid. Further one-third gastric resection with Polya anastomosis for posterior stomal ulcer. Has since remained very well.

CASE E (*Moroney*).—1949 Polya gastrectomy elsewhere (apparently no ulcer was found). 1952 converted to Moroney for intractable dumping. Abdominal vagotomy. 1952 6th–9th left intercostal nerves crushed for severe epigastric pain, without relief. 1953 transthoracic vagotomy (fractional test-meal showed hyperchlorhydria). Histological proof of bilateral vagotomy obtained. One week after operation, test-meal showed achlorhydria. 1957 radiography revealed stomal ulcer. Gastric acidity high. A large stomal ulcer was resected and the anastomosis converted to a Roux-Y type, an abdominal vagotomy was also done. The patient has since remained well.

Discussion

The numbers in this series are small, and in the disappointing cases there was an almost bewildering variety of antecedent procedures. Perhaps the most striking fact is that stomal ulceration following uncomplicated Polya gastrectomies (5 cases) or gastroenterostomy (4) was always completely relieved by transthoracic vagotomy.

Study of the literature suggests that, after gastrectomy, the operation of choice is vagotomy alone, which may be expected to relieve stomal ulceration in three cases out of every four (table II). Our figures support this view with 13 successes in 19 cases. Walters (1959) has suggested that stomal ulceration following gastroenterostomy is somewhat less favourably affected by vagotomy alone (table II) and that in these cases gastric resection is to be preferred. Gastric resection, however, is an operation with its own mortality and morbidity, and we have chosen to try the lesser procedure first. The fact that this succeeded in all 4 indicates that, if the gastroenterostomy is well placed and functioning satisfactorily, transthoracic vagotomy is a sound procedure.

TABLE II—PREVIOUSLY REPORTED RESULTS OF VAGOTOMY FOR STOMAL ULCER

Authors	Cases with previous gastro-enterostomy		Cases with previous gastric resection	
	No of cases	No of failures	No of cases	No of failures
Crile and Brown (1951)	18	3	13	0
Hand and Patey (1953)	2	1	2	0
Wells, B W (1954)	14	10	25	10
Walters Chance, and Berkson (1955)	27	6	78	23
Osnes (1955-56)	5	3	10	0
Knox and West (1959)	5	3	20	3
Davey (1959)	1	0	17	3
Totals	72	26 *(36%)*	165	39 *(23 6%)*

On stomal ulcer after Roux-Y gastrectomy the literature is not informative. Some surgeons are at present performing an elective Roux-Y gastrectomy subtotally without vagotomy for duodenal ulcer, and a proportion of recurrences must surely be expected. A priori thoracic vagotomy should relieve such ulceration. Our own practice has been to employ vagotomy as a routine at the time of the gastrectomy or deliberately across the chest at the same or a second operation in cases of difficulty. Of a series of such operations (Wells and Johnston 1955) stomal ulceration has been suspected in only one. In that one case (which we have mentioned above) the diagnosis was neither confirmed nor disproved; the symptoms were not relieved, but the patient, a chronic alcoholic, has been admitted to a mental institution. Nothing can be deduced except that he was a bad subject for any operation.

Our two cases in which stomal ulceration persisted after thoracic vagotomy are of special interest. It is disturbing that, despite removal of the pyloric antrum and resection of the vagus nerves—attempted and apparently achieved from both below and above the diaphragm, and confirmed histologically—enough acid remained or recurred to provoke further ulceration. How this residual acid was produced remains in some doubt; we do not know whether resection of the nerves was incomplete, whether regeneration took place, or whether a hormonal factor was responsible. But the relapses did in fact occur, and in both cases the ulceration was then apparently relieved by a high gastric resection. This satisfactory end-result presumably excludes the possibility of their being examples of the Zollinger-Ellison syndrome. Possibly the initial antral resections went insufficiently high on the lesser curvature.

Conclusions

1. Transthoracic vagotomy is simple and safe.

2. It is probably the best means of treating stomal ulceration following otherwise uncomplicated gastrectomy, or following gastroenterostomy provided the stoma is well placed and functioning satisfactorily.

3. The diagnostic proof of stomal ulceration is not always easy. Estimation of night secretion, not routinely available at the time of this study, may prove invaluable. Persisting acid is a reasonable indication for vagotomy.

4. On a-priori grounds, vagotomy is necessary in operations of the Billroth I type for duodenal ulcer. If acidity persists after abdominal vagotomy, thoracic vagotomy should be undertaken as an adjuvant.

5. In patients who have undergone bizarre or multiple operations on the stomach and duodenum accurate diagnosis may be difficult. The surgeon must weigh the dangers and complications of a further abdominal operation against the advantages of actually seeing the lesion. In the presence of pain suggestive of ulcer, and of continued night secretion of acid, thoracic vagotomy is safe and worth while.

6. In some late and complicated cases, disappointments are inevitable whatever is done. It is sententious and not really helpful to suggest that the solution lies in more careful selection in the first place.

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HYPOPITUITARY COMA AND PSYCHOSIS

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This case of hypopituitary coma followed by organic psychosis seems worthy of record because the coma was reversed dramatically by treatment and the patient recovered completely from the psychosis

Case-report

A woman, aged 46, was admitted to the London Hospital [L H no 018163] from the Emergency Bed Service on June 11, 1958, with a provisional diagnosis of meningitis

10 years previously, after the birth of her third child whom she breast-fed for 3 days only, her menstrual periods had decreased from 3–4 to 1–2 days, and their frequency from 4 to 7–10 weeks 5 years later, after appendicectomy, menstruation ceased completely Her general health had deteriorated, and she had lost all libido She felt the cold more, and noticed some thinning of her hair

2 days before admission she felt faint on getting up from a hairdresser's chair, but was able to walk home She went to bed, and in the evening felt feverish Next morning her family practitioner found she had a pyrexia of 102°F, but no other abnormal physical signs Later that day her doctor's deputy found her drowsy The following day (June 11) she was stuporose, with neck stiffness

Course in London Hospital

She was admitted at 3 P M on June 11 Her temperature was 101 6°F and her blood-pressure 105/60 mm Hg She was well nourished, and her skin was soft, pale, and dry The hair on her head was soft and normal in distribution, but on her eyebrows and pubes it was scanty, and in the axillæ absent She opened her eyes in response to her name, but she would not obey simple commands, and she resisted examination, responding violently to painful stimuli She had head retraction, but Kernig's sign was negative The central nervous system was otherwise normal Respiration was irregular, and she yawned frequently Some lymph-nodes in the left side of the neck were tender

Lumbar puncture revealed clear cerebrospinal fluid (C S F) under normal pressure, containing 10 lymphocytes per c mm and 40 mg protein and 35 mg sugar per 100 ml The blood-sugar was 38 mg per 100 ml, and the sodium, potassium, and chloride were normal, but the serum-bicarbonate was reduced to 20 mEq per litre Her total white-cell count was 12,700 per c mm (polymorphonuclears 62%), and the erythrocyte-sedimentation rate was 30 mm in the 1st hour (Westergren)

At 8 P M she was given 50% glucose 40 ml and hydrocortisone 100 mg intravenously, without alteration in her level of consciousness A stomach-tube was passed, and 20% glucose 150 ml was given hourly At midnight her blood-pressure had fallen to 90/70 and a solution of dextrose 45% and saline 0 25% was given intravenously At 3 A M the blood-pressure was unchanged, and she responded to pain But at 5 25 A M the systolic pressure had fallen to 70 mm Hg and a solution of noradrenaline 4 mg in normal saline 500 ml was given in the drip At 5 30 A M her blood-pressure had risen to 100/75, and at 5 45 A M (i e, 20 minutes after starting the noradrenaline drip) she spoke her first rational words, saying she was comfortable, without pain, and not feeling cold At 9 A M the blood-sugar was 222 mg per 100 ml

Noradrenaline had to be continued intravenously for 5 days to keep the blood-pressure in the normal range She also had hydrocortisone 550 mg in the first 22 hours, followed by cortisone 150,100, and 50 mg daily in the 1st, 2nd, and 3rd weeks respectively Penicillin was given for 12 days, and vitamin-B complex with ascorbic acid ('Parenterovite') 4 ml daily for a week Subsequent blood-sugar and serum-electrolyte estimations were normal

An electroencephalogram (E E G) on June 18 showed symmetrical rhythmic activity of 5–7 cycles per sec, at a voltage of 30–40 μV, without blocking response to visual attention, suggesting generalised disturbance and slowing of cerebral activity At lumbar puncture on June 16 the C S F contained 4 lymphocytes per c mm and 40 mg protein per 100 ml The chest and skull were normal radiographically

After the period of coma she was uncooperative, attempting to remove the intravenous drip and the nasoœsophageal tube, and she was incontinent most of the time She was deluded, thinking the house physician was her husband and that the nurses were the students' wives On June 27 (16 days after admission) she became violent, shouting and throwing food at other patients, and she was transferred to the Maudsley Hospital

Course in Maudsley Hospital

The patient's mental state fluctuated unpredictably, her behaviour ranging from apathy (when a nurse had to help her to dress) to restlessness, with shouting and aggressive outbursts Her talking ran parallel with her behaviour, and at times she persistently importuned the staff with various requests Her mood likewise fluctuated at first she was usually agitated, tearful, and sometimes suspicious, but later she was more often euphoric Her memory was seriously at fault orientation was always imperfect and sometimes grossly incorrect She misidentified the staff as near relatives, and again thought one of the doctors was her husband She was unable to concentrate on simple tasks for long, and easy calculations were performed either incorrectly or not at all

Her mental disturbance created a considerable nursing problem, but from Aug 8 (2 months after the coma) the fluctuations settled into a calmer, rather foolish, euphoric state She recognised people correctly, and only made moderate mistakes in orientation. On Aug 18 she discharged herself from hospital

Between June 30 and Aug 18, while the patient was taking cortisone, the blood-sugar did not fall below 88 mg per 100 ml, the protein-bound iodine ranged from 3 3 to 5 3 mg per 100 ml and the radioiodine-uptake neck/thigh ratio was 3 (both within normal range), the thyrotrophic hormone was 4 6 milli-units per 100 ml (normal 10–20) The E E G on July 4 still showed symmetrical generalised abnormality, with postcentral activity at 8 and at 6–7 cycles per sec, as well as at 2–4 cycles per sec, all of which now tended to block when the eyes were opened, but by Aug 7 the alpha-rhythm was at 9 cycles per sec, with much less slow activity

Follow-up

Since leaving hospital the patient has been seen regularly, and she has taken cortisone 25 mg daily At first she was still liable to mood changes and her concentration was impaired, but in September, 1958, her husband thought she was better than she had been since her last child was born. She was cheerful and alert, and her libido had returned to normal No abnormality could be detected in her mental state, and she looked very well By October, 1958, she was doing her housework and helping in her husband's shop, being able to calculate quickly and accurately

Discussion

Mechanism of Hypopituitary Coma and Response to Treatment

Many metabolic factors may precipitate coma in patients with hypopituitarism (Caughey 1958), and our patient certainly had an intercurrent infection, hypoglycæmia, and hypotensive changes But hypotension per se, as opposed to postural hypotension, is not mentioned as a cause of coma by Caughey nor by Sheehan and Summers (1952)

Sheehan and Summers wrote "It is not easy to assess the value of treatment of hypopituitary coma, because if the patients are left without treatment some of them recover from the coma spontaneously and some die Thus the only indications of the efficacy of any particular treatment are the rapidity of the clinical response and the proportion of the patients treated in this way who do show a response"

We consider that this patient would have died if noradrenaline had not been given, and that the rise in the level of consciousness from coma to rational spontaneous speech within 20 minutes indicates that hypotension was an important contributory factor in this case Finnerty et al. (1954) showed that a fall in mean blood-pressure of 29–80 mm Hg can cause alterations in consciousness, although variation between individuals is wide

The combined action of hypoglycæmia and hypotension was displayed in a group of schizophrenic patients who—Marley (1956) found—could not be rendered comatose with 400–500 units of soluble insulin but required in addition the hypotensive effect of hexamethonium and the upright posture early in the hypoglycæmic period

Mechanism of Production of Psychosis

If coma was due to altered metabolism of the central nervous system associated with hypotension, hypoglycæmia, and hypocorticism, then the transient organic psychosis is likely to have resulted from damage, albeit reversible, from the same causes

The functional and pathological changes due to hypotension and hypoglycæmia are very similar After operations in which the blood-pressure was below 80 mm. Hg, Berg et al. (1957) showed that disturbances in the E.E.G lasted a few days Permanent and profound mental changes were described by Allison (1956) and Bedford (1957) Similarly, delayed recovery from the effects of hypoglycæmia is well known, the distribution of neuronal necrosis in fatal cases was shown to be similar to that of anoxic lesions (Lawrence et al. 1942) Experimentally Gellhorn et al. (1938) found that both the anoxic stimulus of 6·2% oxygen and that of hypoglycæmia of around 40 mg per 100 ml. were required to produce Cheyne-Stokes respiration in dogs

The relation between the adrenocortical and pituitary hormones and cerebral activity is complex. Depression and paranoid psychoses have been reported in patients with Addison's disease, cortisone or hydrocortisone producing the greatest restoration of mental capacities (Woodbury 1958) Mental torpor, depression, and delusions were often observed in proven cases of hypopituitarism (Sheehan and Summers 1949), and the loss of alpha-rhythm in the E E G in such cases was noted by Hughes and Summers (1956) It seems unlikely in our case that the mental changes were due to excess cortisone, as disorientation is not characteristic of such psychoses, although organic psychosis with delusions and hallucinations due to excess cortisone was recorded by Glaser (1953) But our patient's eventual return to the wellbeing which existed 10 years previously may be attributable to continued treatment with cortisone

The relative contribution of hypotension, hypoglycæmia, and endocrine disturbances in producing coma and psychosis in this case must remain conjectural

Summary

A 46-year-old woman with hypopituitarism was precipitated into coma by an infection and failed to regain consciousness after the administration of glucose and hydrocortisone, but when the fall in her blood-pressure was reversed with noradrenaline intravenously she was able to speak rationally within 20 minutes

After the coma she had an organic psychosis which lasted for 3 months From this she recovered completely

The patient was under the care of Sir Russell Brain and Sir Aubrey Lewis, and we wish to thank them for their encouragement and help with this paper

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PROLONGED DRUG TREATMENT FOR PULMONARY TUBERCULOSIS

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FIVE years ago, Hoyle, Nicholson, and Dawson described the immediate results of treating 142 patients with antituberculous drugs for at least nine months At that time only 63 of the 142 patients had been observed for more than a year after completing treatment, and so the eventual outcome of this form of therapy could not be assessed We review here the progress of these patients over the eight years in which they have been treated and subsequently observed.

Present Investigation

The detailed analyses made for the original study were lost in a fire It is probable that all the patients in that series have been included in the present one, as a systematic review of the records yielded 193 patients fulfilling the requirements for inclusion. This rather larger number is made up by those in our care (C H. and H N) as well as those originally in the care of the late Dr Andrew Morland who were supervised by one of us (H. N)

All patients who received antituberculous drugs for at least nine months before June, 1955, are included. 171 of these patients have been observed for two years, and 134 for three years, after completing drug treatment. 75 of them were treated surgically and by other methods as well as with drugs, but for the other 118 patients, drug therapy was the only definitive treatment. The two groups were similar as regards

TABLE I—EXTENT OF DISEASE AND TREATMENT OF 193 CASES OF PULMONARY TUBERCULOSIS

Extent of disease*	Drugs only	Surgery	Total
I	23	16	39
II	57	42	99
III	38	17	55
Total	118	75	193
Cavitation	60	56	116

* This is classified according to Foster-Carter et al. (1952), class I, not more than one zone in one lung involved class II, unilateral or bilateral disease involving two or three zones class III, bilateral disease affecting four or more zones

the presence of cavitation, but a rather higher proportion of patients treated with drugs alone had extensive disease (table I)

152 patients were receiving antituberculous drugs for the first time 41 had had previous treatment for short periods, regarded as inadequate by present standards, and 35 of these were in the group of 118 patients treated by drugs alone

Radiographic evidence of cavities was established and closure confirmed by tomography in almost all cases Nodules were defined as uniformly dense foci over 1 cm. in diameter, in the plain film or tomograph, whichever was the greater When bacterial resistance was measured the following standards were used

	*Streptomycin**	*P.A S**	*Isoniazid**
Partially resistant	3	2	1·0
Resistant	10	10	5·0

* µg per ml

Progress was measured mainly by bacterial and radiographic methods Sputum concentrates were examined monthly and cultures made until they repeatedly failed to grow *Mycobacterium tuberculosis* Radiographic progress was followed with monthly posteroanterior films The final results of treatment were judged by the ability of patients to resume and continue their normal lives Relapse was recognised by radiographic extension of disease, by the appearance of cavitation, or by return of a positive sputum

TABLE II—DURATION OF DRUG TREATMENT

—	No of patients	Duration of treatment (mos)			
		9–12	13–18	19–24	Over 24
Extent of disease					
I	39	24	6	6	3
II	99	33	24	30	12
III	55	7	19	10	19
Total	193	64	49	46	34
Surgery and artifical pneumothorax	75	33	21	12	9

Methods of Treatment

Drug regimens varied from patient to patient and over the years of the study, but all patients were treated with combinations of two or three drugs accepted as effective The doses used were streptomycin sulphate 1 g daily, combined dihydrostreptomycin 0 5 g and streptomycin 0 5 g daily, *p*-aminosalicylic acid (P A.S) 6 g twice daily, and isoniazid 100 mg twice daily The duration of drug treatment increased over the years mainly because of the evolution of ideas upon prolonged therapy, but it was also influenced by the extent of the disease Patients treated surgically received less drug treatment (table II)

With 1 exception all patients were admitted to hospital and rested in bed for the first three to six months, most of them spent about six months at a sanatorium afterwards Those with cavities were usually nursed with the cavity dependent for the first few months In addition to antibacterial treatment 60 patients were treated surgically and 15 by artificial pneumothorax The indications for additional treatment varied, sometimes withholding this was considered unjustifiable when the results of drug therapy alone were still unknown, especially in dealing with thick-walled cavities which persisted after six months' drug treatment and bed rest there is now little doubt that some of these cavities would have closed after longer treatment with chemotherapy alone (table III)

TABLE III—INTERVALS FROM START OF TREATMENT TO CAVITY CLOSURE

Time of closure (mos)	Drug treatment alone	Drugs plus surgery and other measures
0– 6	30	34
7–12	15	15
13–36	4	4
Total	49*	53
Failure to close	11	3

* In 4 other patients cavity closure was achieved with drugs, but operation was performed subsequently

Results

Sputum Conversion

Myco tuberculosis was isolated from the sputum of 140 of the 193 patients Only 1 patient has a persistently positive sputum after completing treatment, although in 5 others bacilli continued to appear in the sputum for a year, in these the sputum became negative within the next two years while the same drug regimen was continued. Of 118 patients treated with drugs alone, 79 had initially a positive sputum which became negative in all but 1

Cavity Closure

116 of the 193 patients had cavities, which were closed by drugs alone in 53 instances, in the earlier years of the study many patients were treated surgically within a year after drug treatment was started, and for this reason the influence of drug therapy on cavity closure cannot be fully assessed The intervals from the start of treatment to cavity closure are shown in table III

In 30 out of 60 patients treated by drugs alone the cavities closed within six months, and in a further 19 after six months to three years 11 patients in this group were left with persisting cavities, but in only 1 did the sputum remain positive, in 8 the sputum was negative within a year, and in the 2 others within three years

14 patients of the whole series had persisting cavities at the time drugs were stopped 9 of these are alive with

TABLE IV—DATA ON 23 PATIENTS WHO RELAPSED

Case no	Extent of disease	Previous drug treatment	Length of drug treatment	Interval since stopping treatment	Type of relapse *	Sputum	Sensitivity †	Outcome
1	II	–	9 days	Under treatment	Cavity	Pos	Satis	Resection, well
2	III	+	5 mos.	" "	New cavity	Neg		Resection, well
3	III	–	6 "	" "	Cavity	Pos	Res , s	Fistula, dead
4	III	–	7 "	" "	New cavity	Neg		A.P , well
5	II	–	9 "	36 mos	Ext. cavity	Pos	Satis	Thoracoplasty, well
6	I	–	9 "	18 "	Extension	Neg		Drugs, well
7	III	–	11 "	12 "	"	"		No treatment, well
8	II	–	12 "	18 "	Ext. cavity	Pos	Satis	Pulmonary embolism, dead
9	III	–	12 "	48 "	Empyema	"	Satis	No treatment, well
10	III	+	12 "	Under treatment	Extension	Neg		Well at first, later died from respiratory infection
11	I	+	12 "	12 mos	"	"	•	Drugs, well
12	II	–	12 "	24 "	"	"		No treatment, well
13	II	–	13 "	6 "	New cavity	Pos	Satis	A P , well
14	III	+	17 "	18 "	Cavity			Drugs, well
15	III	–	17 "	24 "	Extension	Neg.		Drugs, well
16	III	–	21 "	3 "	Cavity	"		Thoracoplasty, well
17	II	–	21 "	12 "	Nodule enlarged	"		Drugs, excision mucocele
18	II	+	22 "	Under treatment	Extension	Pos	Res , s	Drugs, well
19	II	–	24 "	3 mos	Cavity	"	Satis	Drugs, well
20	III	+	24 "	24 "	Extension	"		No treatment
21	III	–	30 "	12 "	Nil radiologically	"	Satis	No treatment, well
22	III	+	39 "	18 "	Extension	Neg.		No treatment, well
23	III	–	39 ,	30 "	Cavity	"		No treatment, well

* The site was new in case 1, and the original site in the remainder

† Satis indicates full sensitivity to streptomycin (s), P.A.S., and isoniazid

open cavities and a negative sputum, but 6 had a positive sputum at the end of treatment or subsequently, 3 have died of tuberculosis and 1 of respiratory failure.

Nodules

Of the 193 patients 35 had nodules, which were resected in 12. The other 23 all progressed satisfactorily under treatment with drugs alone. In 5 the lesions disappeared rapidly, and in 12 they shrank gradually and formed a linear shadow, in 5 the nodules remained the same size, and in 1 the progress could not be assessed adequately. 16 of the 23 patients have been followed for over three years after completing antituberculous drug therapy, and in no instance did cavitation occur within the solid lesion. of the 12 patients treated by lung resection only 2 received this sort of therapy because of cavitation within the nodule.

Relapse

Of the 193 patients, 23 (12%) relapsed from the beginning of treatment up to four years after drugs were stopped. (6 of these patients relapsed while receiving chemotherapy, but 17 [8%] relapsed after drug treatment was completed.) Of 118 patients treated with drugs alone, 3 relapsed during treatment and 15 (13%) relapsed subsequently. Details of these patients are given in table IV.

Of the 23 patients who relapsed, 13 had advanced disease and 8 had disease of moderate severity (table IV). 15 of the 23 had received nine to fifteen months' drug treatment and relapse occurred up to four years after treatment was stopped. 8 patients relapsed who had had over eighteen months' continuous drug treatment. The interval between discontinuance of drug treatment and relapse ranged from three months to four years, in 6 patients the interval was over two years.

19 of the 23 patients who relapsed are now well, with their disease stabilised. 5 of them were treated surgically and 2 had an artificial pneumothorax. 6 received further chemotherapy for about two years, while the remaining 6 were not given any further treatment but have remained well. 1 other patient is at present receiving further chemotherapy. The remaining 3 patients of the 23 who relapsed have died—2 from non-tuberculous causes and 1 from advanced tuberculosis of many years' standing.

Deaths

11 patients died during the eight years of observation—5 from tuberculosis, 3 from respiratory failure, and 3 from unrelated causes.

Drug Toxicity

60 of the 193 patients complained of symptoms attributed to antituberculous drug (table V). Vestibular symptoms usually disappeared when streptomycin was discontinued. Other side-effects were controlled with appropriate treatment, and therapy was usually not curtailed.

Outcome in 134 Patients Followed for Three Years after Completion of Drug Treatment

123 of the 134 patients have survived. 6 have open cavities but are well with a negative sputum, 17 have relapsed at some time within the three years, and 6 have severe breathlessness with bronchitis and are respiratory cripples. 116 are well and have resumed work.

Return to Work

Of 174 cases where records are available, 106 patients had returned to work in a year or less, 61 in two years, and 7 after more than two years.

TABLE V—SIDE-EFFECTS OF DRUG TREATMENT

Drug	Side-effect	No of cases
Streptomycin	Tinnitus	2
	Giddiness	14
	Deafness	2
	Drug rash and fever	17
P.A.S.	Drug rash and fever	10
	Goitre	1
	Severe nausea	12
Isoniazid	Burning feet	1
Uncertain	Angioneurotic œdema	1

Discussion

The aims of antituberculous drug therapy are to achieve maximum resolution and permanent healing of the disease. Clinically these may be measured by negative sputum-cultures, closure of cavities, the patient's capacity to lead a normal life and the absence of relapses.

In the present group of patients the outcome with regard to sputum conversion has been very satisfactory. Of the 79 cases treated by drugs alone in which the sputum was initially positive, all but 1 became negative, although in some cases the sputum ceased to be positive only after many months of drug treatment, and in 5 instances sputum conversion was achieved after more than a year of continuous chemotherapy.

For reasons already discussed, we are unable to assess the effectiveness of antituberculous drugs in closing cavities, but we should like to emphasise that cavity closure after six months' therapy occurred in about a third of those cases treated with drugs alone. Failure to achieve cavity closure at six months should not be regarded as failure of chemotherapy. Cavitation persisting with a negative sputum has not in our series proved to be a precursor of relapse, but numbers were small. However, Raleigh (1957) suggests that this may be so, 50% of his 123 patients with negative sputum and persisting cavities relapsed over a period of two and a half years, following an average of sixteen months' treatment. If cavities persist and surgery is excluded, it is probably wise to continue antituberculous drug treatment beyond two years. Persisting cavitation in association with a positive sputum proved as serious as expected, in that 4 out of 6 such patients died.

In this series there are 182 surviving patients, and 174 are leading normal lives. 6 have chronic bronchitis and various degrees of respiratory failure impairing their capacity for work. Of 134 patients followed for over three years after stopping chemotherapy, 122 have survived and been rendered non-infectious, but complacency is dispelled when the numbers of patients who have relapsed are considered. Unfavourable radiological change or positive sputum occurred in 23 of the 193 patients—about 12%. Of these 23 patients, 7 had had previous chemotherapy and 7 were longstanding cases of pulmonary tuberculosis and had received various other treatments in the past. Among these patients who relapsed, radiological extension of the disease with cavitation was seen most frequently, in fewer patients extension occurred without cavitation. Spread of the disease to a new site or the finding of a positive sputum in the absence of radiological change was rare. 8 patients relapsed after receiving chemotherapy for more than eighteen months. 1 patient was known to have taken the drugs irregularly. Another had pneumoconiosis complicated by tuberculosis, while a further patient was found to have a mucocœle of the bronchus but no definite evidence of tuberculosis. In the 4th patient cavity closure was believed to have occurred within three months of starting treatment, subsequently three months after treatment was stopped tomography demonstrated a cavity in the original situation, casting some doubt on the completeness of the first tomographs. The 5th patient had a persisting cavity under a thoracoplasty with a positive sputum. On routine tomography the 6th was found to have unsuspected rarefaction in a nodule approximately a centimeter in diameter, no further treatment was given, and a year later tomography disclosed a small stellate shadow at the site of rarefaction. 2 patients had had previous inadequate chemotherapy before their definitive course, and afterwards developed slight extension of their disease. 1 patient is at present under treatment, but the other 7 have done well and are living normal lives with their disease apparently stabilised. In general the outcome in patients who relapsed is satisfactory in that 19 of 23 are well with their disease inactive.

Microbial persistence must be the ultimate reason for failure of chemotherapy (McDermott 1958). At a clinical level, several factors are important. Patients may fail to take the drugs prescribed, and this is now a well-recognised difficulty in long-term ambulant therapy. Gastrointestinal symptoms, so frequently produced by P.A.S., are particularly important in this respect. The importance of drug-resistant organisms has been stressed by Ross et al. (1958), but in our group drug resistance was infrequent. Usually it was found in those patients who had had previous inadequate chemotherapy. Previous treatment, however, may prejudice future chemotherapy in other ways as yet undetermined, encouraging microbial persistence without causing insusceptibility to drugs as shown by in-vitro methods (McDermott 1958). The length of time during which drugs should be given remains obscure. Ross et al. (1958) report a trend towards an inverse relationship between relapse and duration of treatment, but 63 of their patients treated for more than eighteen months had not relapsed at the time of their report, though the period of follow-up of these patients was only eighteen to thirty months. Smart and Gough (1958) reported no instances of relapse in a group of 75 patients who received chemotherapy for over a year, but the majority of their patients (45/75) were followed for less than two years after completing treatment. Relapse has, however, been observed in patients who have received two years' continuous drug therapy, both in the present and in other series (Raleigh 1957). This fact, together with the finding of drug-susceptible organisms in some of these cases, suggests that two years' treatment is sometimes insufficient. In our view all cases of active pulmonary tuberculosis, even when very slight, should receive at least two years' drug therapy.

Summary

The progress of 193 patients with pulmonary tuberculosis who received at least nine months' antibacterial drug treatment before June, 1955, has been reviewed.

The duration of treatment was over eighteen months in 80 patients, and 118 were treated with drugs alone. 134 were followed for more than three years after completing treatment.

At completion of treatment sputum culture for *Myco. tuberculosis* was negative in all patients except 1.

Of 60 patients with cavities who were treated by drugs alone, the cavities closed in less than six months in 30. In a further 19 the cavities closed after persisting for from six months to three years.

In each of 23 patients with nodules treated by drugs alone, the progress was satisfactory. 16 of these patients were followed for over three years after completing treatment.

12% of the whole group relapsed between the beginning of treatment and up to four years after drug treatment was discontinued. Of 118 patients treated with drugs alone, 13% relapsed after treatment was stopped.

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TRANSPOSITION OF THE VISCERA AND STERILITY IN MEN

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TRANSPOSITION of the viscera may be partial or complete. In 1947 Torgersen collected 129 cases, 123 of which were complete.

The reported frequency differs. In necropsy material it has been found to be 1 in 6000 and in a mass chest survey 1 in 6500 (Blegen 1949). Torgersen (1947) found that the frequency was 1 in 8000–10,000. Familial occurrence has been reported several times (Call and Woolf 1934, Cockayne 1937, Feldmann 1935, Feldmann and Needle 1934, Torgersen 1947 a and b). Torgersen reported consanguinity in 7.3% of the cases. Published accounts seem to indicate that cases may occur in the line of ascent and descent (Doolittle 1907, Torgersen 1947 a and b).

The ætiology is unknown. It has been suggested that the anomaly may be related to twins one of which has been absorbed in utero.

As regards external signs Ebstein (1923) reported that the right half of the scrotum hung further down than the left in 28 out of 36 men with complete transposition of the viscera. Left-handedness is not believed to be commoner in persons with visceral transposition than in others (Cockayne 1937).

The diagnosis may be made by percussion or auscultation, but should be confirmed by electrocardiography and by X-ray examination of the chest and gastrointestinal tract (Wood and Blalock 1940).

So-called Kartagener's syndrome is said to be common in these cases. It consists in visceral transposition, bronchiectasis, and malformation of the nasal sinuses (Cockayne 1937, Karani 1952). Torgersen (1947) found bronchiectasis in 8% of his cases.

No mention seems to have been made of sterility or reduced fertility in cases of visceral transposition.

Present Series

My series consists of 4 cases (3 male and 1 female) of complete visceral transposition among two sibships. Consanguinity in a high degree is present, the fathers are brothers and the mothers sisters, so the children are double first cousins. In addition, the parents have common greatgrandparents (fig. 1).

Of external signs which might indicate visceral transposition, in all 3 men the right half of the scrotum hangs lower than the left and 2 of them are left-handed. There are no other external peculiarities, and all the men are of masculine build.

All have a history of mild attacks of asthma, their colds have tended to be lengthy with much expectoration. 1 of the men has undergone an operation for frontal sinusitis, and another has diabetes mellitus. The woman has had an operation for acute appendicitis, and the appendix was found to be localised to the left side of the abdomen.

Electrocardiographic tracings showed in all cases total inversion of lead I and transposition of leads II and III (fig. 2).

Radiography in case D (see fig. 1) showed the liver in the left side of the abdomen, and total inversion of the stomach and colon was found after administration of contrast medium, chest radiography revealed complete transposition of the heart (figs. 3–5).

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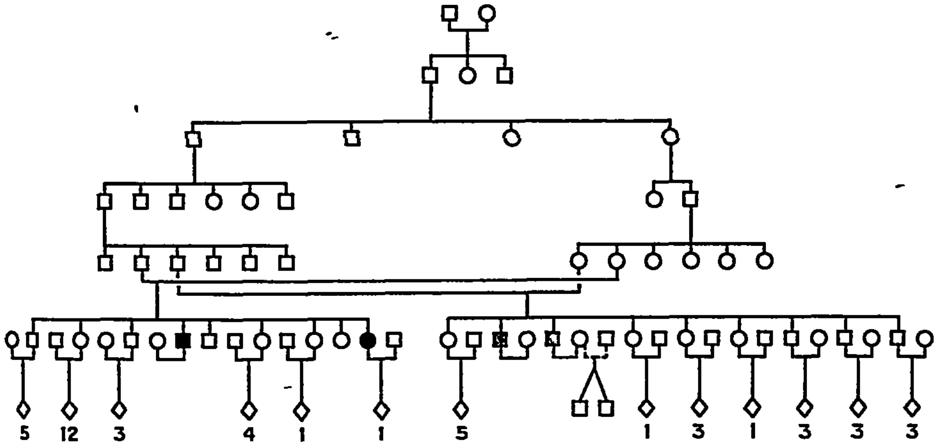

Fig 1—Family tree showing two sibships of 9 members each In one there is 1 man and 1 woman and in the other 2 men with complete transposition of the viscera

Other members of the family, who were scattered all over the country, have been examined, nearly all were examined by electrocardiography and chest radiography and the remainder only by percussion and auscultation and, in males, inspection of the scrotum No sign of visceral transposition was detected

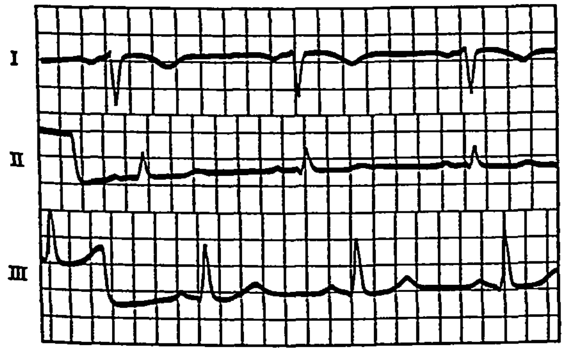

Fig 2—Case D electrocardiogram showing total inversion of lead I and transposition of leads II and III.

The family tree (fig 1) shows 9 siblings in each sibship All who are married have children except the men with visceral transposition, whereas the woman with visceral transposition has 1 child Moreover, 1 of the men—case D—is married to a woman who has 2 sons born prior to the present marriage

I tried to investigate the affected men as regards fertility But 2 of them were over 50 years of age and so were their wives, and they refused to be examined The 3rd man (case D), however, is married to a woman of child-bearing age, who had given birth to 2 sons before the present marriage, and they want children, so he declared himself willing to be examined

Dr Richard Hannen investigated case D's semen The specimen consisted of 3 5 ml of rather viscid, slightly transparent seminal fluid. Three-quarters of an hour after ejaculation 91% of spermatozoa were immobile, the survival-time was less than twenty-four hours after the ejaculation Spermatozoa numbered 95,000,000 per ml and the total number 333,000,000, 47% had abnormal head shapes Dr Hammen concluded that fertility was much reduced

The genitalia appeared normal except for the right half of the scrotum hanging lower than the left, the testes were walnut-sized and firm

A biopsy specimen of the right testis (examined by Dr H. Olesen) contained particles of testicular tissue with numerous tubules, most of these were of normal width, but a few were somewhat narrow with mild fibrous thickening of the tubular walls Throughout, they were lined with very tall columnar epithelium, containing all elements and with very brisk spermiogenesis, but some spermatozoa were thin with somewhat pear-shaped heads There were no clear degenerative changes of the epithelial tissue The interstitial tissue was sparse, with very small groups of Leydig cells, no inflammatory reaction Dr H. Olesen concluded that the testicular tissue showed slight degenerative changes and brisk, somewhat abnormal spermiogenesis

Basal metabolic rate +11% (determined twice) Hormone analyses Gonadotrophins below 50 milli-units, total and fractionated 17-ketosteroids normal

The cases in this family suggest that men with transposition of the viscera may be infertile or subfertile This point should be further investigated in other patients with the condition, and, if confirmed, a watch should be kept for transposition of the viscera among patients at male sterility clinics

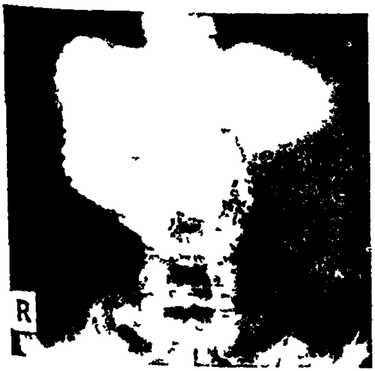

Fig 3—Case D X-ray film after barium meal showing stomach on the right side.

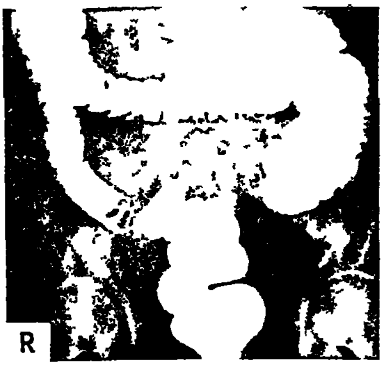

Fig 4—Case D X-ray film of colon after barium enema showing ascending colon on left and descending colon on right.

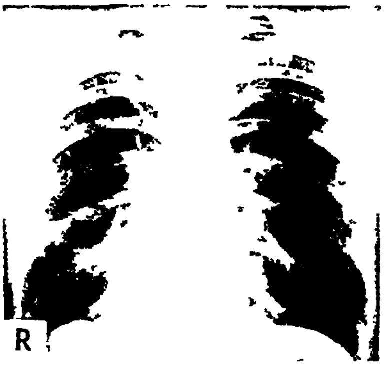

Fig 5—Case D chest radiograph showing transposition of heart.

Summary

Two sibships, each of 9 members, includes 4 cases of transposition of the viscera (3 men and 1 woman)

There is a high degree of consanguinity, as their mothers are sisters and their fathers brothers, and the parents have common greatgrandparents All except 1 woman and 1 man are married, and all those who are married have had children except the men with visceral transposition 1 of these, married to a woman who had borne 2 sons before the present marriage, was investigated more closely, examination of seminal fluid and biopsy of the testis suggested reduced fertility

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PRODUCTION OF VIRÆMIA IN CORTISONE-TREATED MONKEYS WITH THE ATTENUATED BRUNENDERS STRAIN OF TYPE-1 POLIOVIRUS

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Much of the information on the infectivity for monkeys of the strains of poliovirus used for the production of formalin-inactivated vaccines has been obtained from investigations with virulent strains (Bodian 1956, Eklund et al 1956, Gebhardt and Bachtold 1956, Syverton et al 1956) In Britain, however, the attenuated Brunenders strain of poliomyelitis virus is used as the type-1 component of poliomyelitis vaccine (Biological Standards Control Laboratory 1957) and information on the infectivity of this strain for monkeys was required so that satisfactory procedures could be adopted for testing vaccines manufactured in this country A series of experiments was carried out, therefore, in which cortisone-treated cynomolgus monkeys were injected with varying doses of the Brunenders strain These experiments provided information on the occurrence of viræmia and on the ability of the strain to produce lesions in the central nervous system

Materials and Methods

Animals

Cynomolgus monkeys (*Macaca irus philippinensis*) weighing between 1 4 and 1 8 kg were used They were in good condition and had been in quarantine for at least a month before use Before injection of virus each animal was anæsthetised by an intraperitoneal injection of pentobarbitone sodium and also given 300,000 units of long-acting penicillin and 0 4 g of chloramphenicol intramuscularly All monkeys were given 150 mg cortisone intramuscularly 2 days before injection of virus, and 100, 50, 75, 50, 50, 75, 50, and 50 mg respectively at 0, 2, 4, 7, 9, 11, 14, and 16 days thereafter

Inoculation of Virus

Suspensions of living virus were prepared in either commercial poliomyelitis vaccine or medium 199 (Morgan, Morton, and Parker 1950) as described previously (Coid, Beswick, and Tobin 1960) The total dose of virus given to each monkey varied between 3 and 140 TCID$_{50}$ and was contained in a volume of 3 4 ml, each animal receiving 0 3 ml into each thalamus, 0 1 ml into each of three lumbar segments, and 2 5 ml into the right deltoid muscle

TABLE I—TIME AFTER INJECTION WHEN VIRUS WAS FIRST ISOLATED FROM THE SERA OF MONKEYS INJECTED WITH TYPE-1 POLIOMYELITIS VIRUS

Virus suspended in	No of serum samples in which virus was first isolated (days after injection)				Total
	3	7	10–11	15–18	
Poliomyelitis vaccine	4	2	2	4	12
Medium 199	1	7	3	2	13
Total	5	9	5	6	25

Isolation of Virus from Blood-serum

Blood samples were taken from the femoral vein at intervals between the 3rd and 18th day after injection and from the heart at the time of death Virus was isolated from the serum using monkey-kidney cell cultures by the method previously described, and all isolates were typed to confirm that they were type-1 poliovirus (Coid, Beswick, and Tobin 1960)

Histological Examination

At the end of the observation period, which varied from 21 to 25 days, or at the time when paralysis developed, the animals were anæsthetised with pentobarbitone sodium and perfused with formol-saline, and the brains and spinal cords were removed for histological examination (Biological Standards Control Laboratory 1957)

Results

A total of sixty-eight monkeys were injected over a period of approximately 18 months, forty-one receiving virus suspended in poliomyelitis vaccine and twenty-seven virus suspended in medium 199 Viræmia was detected in twenty-five monkeys—in twelve of those receiving virus in vaccine and thirteen of those receiving virus in medium 199 In sixteen of the twenty-five monkeys virus was isolated on one occasion only and in the remaining nine at least twice from consecutive blood samples The results, giving the time at which virus was first isolated from the blood, are shown in table I It is evident that the first isolations did not occur at any particular time after injection and that there is no obvious difference in the results obtained with virus in vaccine and virus in medium 199 It is interesting to note that 6 of the first isolations occurred as late as between 15 and 18 days after the injection of virus, and of these 2 were isolated actually on the 18th day The levels of virus found in monkeys injected with the highest dose of virus varied from minimal amounts to 10^{1} TCID$_{50}$ per ml

In table II these results are compared with those obtained by histological examination When the results of both tests are taken together it is seen that thirty-three monkeys gave evidence of infection, in eight there was histological evidence only, in twelve serological evidence, only and in thirteen both histological and serological

TABLE II—COMPARISON OF VIRÆMIA WITH HISTOLOGICAL EVIDENCE OF INFECTION IN MONKEYS INJECTED WITH TYPE-1 POLIOMYELITIS VIRUS

Virus suspended in	No of animals with			Total no of animals infected
	C.N.S lesions only	Viræmia only	Viræmia and C.N.S. lesions	
Poliomyelitis vaccine	5	7	5	17
Medium 199	3	5	8	16
Total	8	12	13	33

evidence Therefore, if histological examination alone had been made infection would have been detected in only twenty-one monkeys, and if serological examination alone had been made only twenty-five would have shown infection Again, there was no obvious difference in the results obtained with virus in vaccine and virus in medium 199

Conclusions

In the safety testing of inactivated poliomyelitis vaccine in monkeys it is important that the procedures adopted should ensure that no chance of detecting the presence of live virus is missed The experiments described, using the attenuated Brunenders type-1 strain, have shown that combining the histological examination of the central nervous system with the examination of the blood for the presence of virus is more satisfactory in detecting infection than either method alone

It is evident also that if infections are not to be missed the examination of blood samples must be made at regular intervals during the observation period and at least up to the 18th day

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VITAMIN-A DEFICIENCY FOLLOWING TOTAL GASTRECTOMY

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The operation of total gastrectomy is relatively rare and is often followed by digestive and other complications The sequelæ of the operation have been much investigated, but we have been unable to find any record of vitamin-A deficiency, with dermatological lesions or impaired night vision, developing after this operation In the course of a long-term study of the metabolic effects of total gastrectomy the five patients described in this paper were all found to be deficient in vitamin A.

Material and Methods

Total gastrectomy, with œsophagojejunal anastomosis, was performed for histologically proven carcinoma in cases 1, 3, and 5 and for gastric stenosis due to corrosive gastritis in case 4, a tiny fringe of fundus was left to facilitate the anastomosis after the removal of a clinically malignant, but histologically benign, gastric ulcer in case 2, who also underwent partial pancreatectomy and who later developed diabetes mellitus At the time of this study there was no evidence of recurrent carcinoma in cases 1, 3, and 5

TABLE II—RESULTS OF VITAMIN-A-ABSORPTION TESTS

Case no	Relation to treatment	Serum-vitamin-A levels (μg per 100 ml)			
		0 hr	2 hr	4 hr	6 hr
1	Before	9	—	40	—
	After	30	20	155	65
2	Before	13	—	95	—
	After	33	258	370	358
4	Before	8	—	40	—
	After	40	35	165	90
5	Before	12	—	50	—
	After	46	248	190	89

Serum-vitamin-A concentrations were estimated by the method of Kaser and Stekol (1943)

Vitamin-A-absorption tests were carried out in four cases after an 8-hour fast. A fasting blood sample and further samples at 2, 4, and 6 hours after approximately 200,000 I U vitamin-A palmitate in olive oil (7 ml. 'Avoleum', B D H) orally were collected, no food being permitted during the test The absorption tests were repeated after treatment with oral vitamin A 100,000 I U daily for 2–3 weeks

Dark-adapted visual acuity was assessed before and 2–3 weeks after treatment with oral vitamin A, by the method of Riddell (1940, 1943), the examiner being unaware of any treatment given, or of the biochemical findings

Jejunal biopsies were obtained, without overt bleeding, using a biopsy tube (Wood et al 1949) passed under radiological control Specimens were fixed immediately in 10% formol-saline followed by formol-corrosive, and paraffin sections were stained by hæmalum and eosin, trichrome stains, mucicarmine (Southgate), van Gieson, diazo (Pearce), reticulin (Gordon and Sweet), and periodic-acid Schiff reagent.

Fat absorption was assessed over a 4-day (case 3) or 10-day balance period, the daily intake of fat being 50 g

A detailed dietary history was obtained by standard methods, particular reference being paid to the carotene and preformed vitamin-A content of the diet.

Results

Vitamin A—The results of the biochemical studies are given in tables I and II The initial value (table I) refers to the vitamin-A concentration of serum obtained from the patients when they first came under observation and stored at −20°C until analysed In four cases vitamin-A absorption tests (table II) were carried out and the estimations were made immediately The fasting values were subnormal in all cases, and, although there was evidence of absorption shown by a rise in the serum-vitamin-A concentration, the peak values were less than those obtained in normal subjects When the tests were repeated after oral treatment with vitamin A the fasting concentrations and peak values were then normal

Dark-adapted vision—Before treatment dark-adapted vision was subnormal in four cases (table I), three of whom were retested after vitamin-A therapy and all had returned to normal In the fifth case dark-adapted vision

TABLE I—DATA ON 5 CASES OF VITAMIN-A DEFICIENCY FOLLOWING GASTRECTOMY

Case no	Age (yr)	Sex	Time since operation (yr)	Fat absorption (%)	Daily vitamin-A intake (I U)	Initial serum-vitamin-A level (μg per 100 ml.)	Skin lesions	Dark-adapted visual acuity	
								Before treatment	After treatment
1	48	F	$5^{1}/_{4}$	54	4368	4		Subnormal	Normal
2	42	M	5	79	5360	9		"	"
3	47	M	2	90	3178	4		"	Not tested
4	60	M	13	68	5590	3	+	Normal	Normal
5	47	M	$1^{1}/_{2}$	76	6413	10		Subnormal	"

was normal this patient had follicular hyperkeratosis of the type described in vitamin-A deficiency

Fat absorption —The amount of dietary fat absorbed was much impaired in three cases, and in the other two was just below the usually accepted lower limit of normality (table I)

Jejunal biopsies —In all instances the appearances of the jejunal mucosa obtained was considered to be within normal limits although minor variations were occasionally noted, such as slight widening of the villi (case 1) and slight reduction in total mucosal thickness (case 4)

Diet —In all cases the intake of vitamin A was within normal limits The bulk of the total vitamin A ingested was in the form of the preformed vitamin The intake of vitamin A in table I refers to preformed vitamin A only

Discussion

There is good evidence that all of these patients were suffering from vitamin-A deficiency All had very low serum-vitamin-A concentrations, and these were raised to normal in the four cases given oral vitamin A, the defective dark adaptation demonstrated in four patients was corrected by oral vitamin A in the three patients who were retested, the one patient who had normal dark adaptation had follicular hyperkeratosis which was cured by oral vitamin A None of the night-blind patients were aware of the defect, but this was not unexpected as all were city-dwellers Follicular hyperkeratosis due to vitamin-A deficiency is extremely rare in this country (Bicknell and Prescott 1953)

The ideal intake of vitamin A is not known with certainty, but a daily intake of 2500 I U is considered satisfactory (Medical Research Council 1949), and we accept that all these patients had an adequate intake well within normal limits No patient took liquid paraffin, which hinders the absorption of vitamin A, and no patient had any intercurrent disease in which vitamin-A deficiency is known to occur as a complication, diabetes mellitus no longer being considered to be a cause of perverted vitamin-A metabolism (Bicknell and Prescott 1953, Moore 1957) Under these circumstances, and because the operation was performed for different lesions, it is difficult to escape the conclusion that the deficiency is, in some way, the result of the operation One patient, not included in this series, had a normal serum-vitamin-A concentration prior to total gastrectomy and one year after operation, this suggests that the deficiency is a late result of operation possibly due to depletion of body reserves and not an immediate metabolic consequence such as might happen in pneumonia

The cause of the deficiency is an interesting problem From what is known of the biochemistry of fat and vitamin-A absorption it is reasonable to suppose that the absorption of vitamin A would be reduced in direct proportion to the degree of fat malabsorption When fat absorption is normal or only slightly impaired, and when the dietary intake of vitamin A is high, as in cases 2 and 4 in particular, it is unreasonable to ascribe the vitamin-A deficiency solely to steatorrhœa Of the cases reported here, there is only one (case 1) in which steatorrhœa alone might possibly have caused the vitamin deficiency

The view that steatorrhœa per se is a cause of vitamin-A deficiency is based largely on study of patients with gluten-induced enteropathy, many of whom fail to absorb vitamin A as judged by the test used here, but in such patients there is an anatomical abnormality of the small bowel which may be the cause of the malabsorption of both fat and vitamin A In our cases there was no evidence of any lesion comparable to that seen in gluten-induced enteropathy and sometimes seen in other types of steatorrhœa (Paulley 1954, Doniach and Shiner 1957, Sakula and Shiner 1957, Shiner 1957, 1959, Butterworth and Perez-Santiago 1958) In two cases only (cases 1 and 4) there were minor histological variations which we do not regard as differing significantly from normal, similar changes were seen in control biopsy material and were obviously the result of processing This is in keeping with the general experience of those who have studied the jejunum microscopically after subtotal gastrectomy Baird and Dodge (1957) found that the jejunal mucosa was normal in twenty-three out of thirty-one patients after partial gastrectomy, the remaining eight cases showing minor variations only After partial gastrectomy Doniach and Shiner (1957) found abnormalities in the jejunal mucosa of one of their four cases, while in a series of fifteen patients with post-gastrectomy steatorrhœa described by Shiner (1959) jejunal villous atrophy, partial or subtotal, was observed in only two cases Paulley (1959) attaches more significance to minor variations than do others It is to be noted that three of our samples (cases 1, 2, and 4) were obtained after the patients had been treated for post-gastrectomy megaloblastic anæmia, and since it is known that atrophic villi may regenerate after therapy in cases of steatorrhœa, other than the gluten-induced variety, it is perhaps possible that significant changes might have been found had the samples been taken before therapy, the clinical condition of the patients did not permit this

The limitations of the absorption test as a means of estimating the degree of absorption of ingested vitamin A in the same individual, as well as between individuals, are well known (Hillman and Becker 1957, Volwiler 1957), but it does appear that our patients can absorb at least some of the large dose of vitamin A used in the test The low peak values obtained in the initial tests, while the patients were in a grossly deficient state, may represent rapid clearance of the absorbed vitamin to body tissues—a feature not evident when the tests were repeated after a period of treatment when the body stores would have been replenished

The cause of the deficiency in these patients with normal dietary intakes, normal histological appearances of the small bowel, and apparently normal absorption of massive doses of vitamin A is obscure, but may well lie in a multiplicity of factors resulting from the operation which act to the detriment of the absorption of physiological amounts of vitamin A but do not apparently hinder absorption of massive amounts, as far as can be judged by the test used

Relatively little is known with certainty about the site of absorption and the factors governing the absorption of vitamin A in man even when the gastrointestinal tract is intact There is good evidence that the site of maximal absorption in rats and ruminants is in the upper small bowel (Popper and Volk 1944, Eden and Sellers 1949) and there is some evidence that this may be so in man (Fingerland 1957) What is known of the factors governing absorption is based largely on the results of absorption tests of the type used here and is therefore liable to misinterpretation

An adequate intake of fat in the diet and the presence of lipolytic enzymes in bile appear to be necessary for the normal absorption of vitamin A, while decreased intestinal motility apparently impairs absorption (Bicknell and Prescott 1953, Moore 1957) All our patients had a normal fat intake The most obvious abnormality in our patients is the loss of the reservoir and digestive function of the stomach with consequent premature passage of a large mass of inadequately digested food relatively low down in the small bowel and rapid transit through the small bowel past the absorbing sites We have been impressed by the very rapid transit of a barium bolus in our patients

Other factors which may also be important are the limited time available for mixing of the bolus with, and digestion by, pancreatic enzymes before the mass reaches the absorbing site, the limited amount of pancreatic enzymes and bile which will be available particularly where the anastomosis is œsophagojejunal rather than œsophagoduodenal (notably where partial pancreatectomy has also been performed as in case 2), and finally the unknown quantity of abnormal bacterial proliferation in the small bowel. Until an absorption test using physiological quantities of vitamin A is devised, it is unlikely that the precise cause of the deficiency will be found

The deficiency of vitamin A in our patients does not seem to be a very severe matter in itself, and it does not seem to be comparable to the gross degrees which cause keratomalacia. Nevertheless we cannot regard the deficiency as other than detrimental to good health, and it would seem desirable to give vitamin A to patients after total gastrectomy as a prophylactic measure On the basis of the present investigations, which are continuing, a course of oral vitamin A, 100,000 I U daily for 2 weeks every six months, seems advisable. On this regime there is no risk of the toxic effects which might result from large daily doses for long periods

Summary

Five cases of vitamin-A deficiency in patients who had undergone total gastrectomy are reported Four of the patients were night-blind and the fifth had follicular hyperkeratosis These abnormalities were corrected in the four cases given oral vitamin A

The deficiency is of complex origin, and steatorrhœa is not the only causal factor

Vitamin A should be administered prophylactically to patients who have undergone gastrectomy

We are grateful to Dr J A. W McCluskie, Prof D F Cappell, Prof W J B Riddell, and Dr E B Hendry for advice and criticism, and to Dr A C Macdonald and Dr D Horne for facilities at the Vale of Leven Hospital, to Mr Arthur Ness, of the department of biochemistry, Western Infirmary, Glasgow, for the serum-vitamin-A estimations, and to Miss M. G McCombie, of the dietetic department, for the dietary histories, and to the physicians and surgeons of the Western Infirmary who have allowed us to study their patients

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Preliminary Communication

THE REJECTION OF RENAL HOMOGRAFTS INHIBITION IN DOGS BY 6-MERCAPTOPURINE

FOLLOWING the report by Schwartz and Dameshek[1] that 6-mercaptopurine can make rabbits tolerant to human serum albumin antigen, I have used this drug in an attempt to modify the rejection of renal homografts in dogs

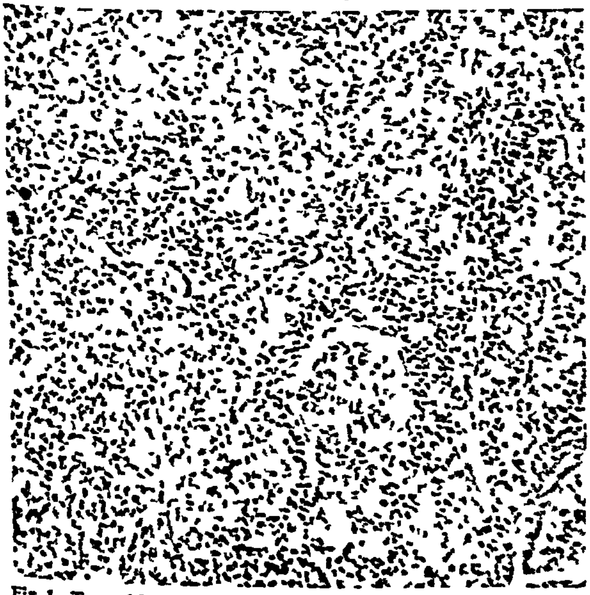

Fig 1—Typical homograft reaction with intense cellular infiltration in a kidney 10 days after transplantation (Hæmotoxylin and eosin. ×120)

INVESTIGATION

The donor and recipient dogs were of different breeds Under intravenous pentobarbitone anæsthesia, a kidney was removed from the donor and transplanted to the right iliac fossa of the recipient, the renal vessels of the donor's kidney were anastomosed to the iliac vessels of the recipient and the ureter was implanted into the bladder

Given by intramuscular injection, in a dosage of 6 mg per kg body-weight daily from the operation, 6-mercaptopurine proved highly toxic. On the other hand, though the animals died from its effects in 10–14 days, they showed no signs of the homograft reaction described by Dempster[2] and Simonsen et al.[3] (fig. 1) On a lower but still toxic dosage in a dog

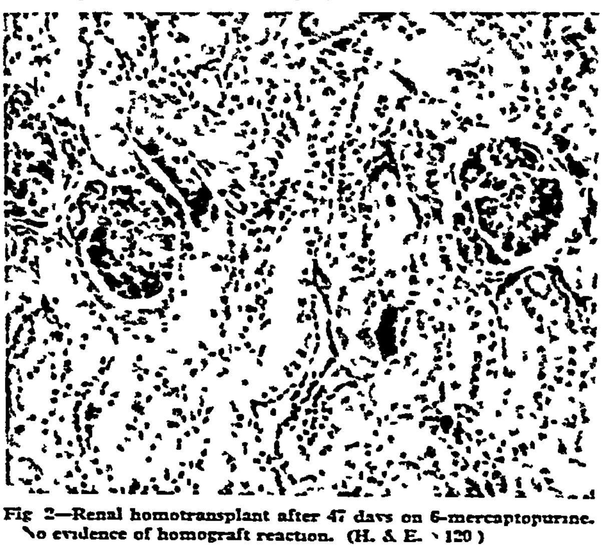

Fig 2—Renal homotransplant after 47 days on 6-mercaptopurine. No evidence of homograft reaction. (H. & E. ×120)

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[1] Schwartz, R., Dameshek, W *Nature, Lond* 1959, 183, 1682

[2] Dempster, W J *Brit J Surg* 1953 40 447

[3] Simonsen M, Buemann J, Gammeltoft, A., Jensen, F, Jorgensen, K *Acta path microbiol scand* 1953, 32, 1

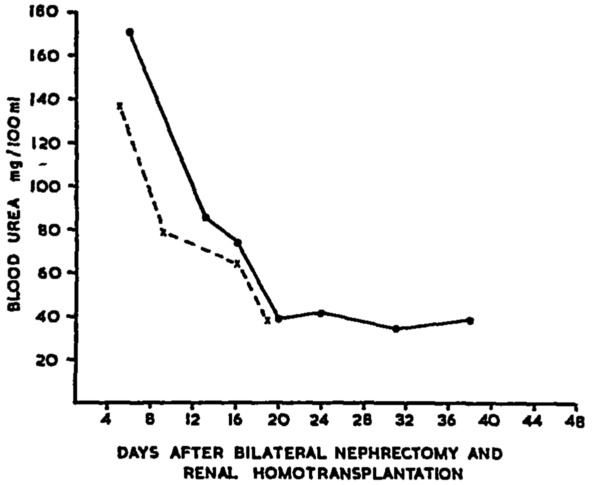

Fig 3—Blood-urea levels in dogs surviving 21 and 47 days after bilateral nephrectomy and renal homotransplantation

which had been off 6-mercaptopurine for six days owing to leucopæmia there was evidence at 12 days of cortical cellular infiltration, which was regarded as a mild homograft reaction.

In a second series of experiments, in order to assess the function of the transplanted kidney, bilateral nephrectomy was performed at the same time as the renal homotransplantation The dosage of 6-mercaptopurine was 5 mg per kg intramuscularly for the first 2 days, 2 5 mg per kg intramuscularly for the next 4 days, and then 2 5 mg per kg daily by mouth except when the total white-cell count fell below 5000 per c mm.

Several dogs on this regime died with oliguria 4–6 days after operation No homograft reaction was found in the kidneys Their death was thought to be due to a vicious circle of primary anuria, uræmia, and vomiting, leading to prerenal uræmia

The two dogs surviving this critical period died of pneumonia, on the 21st and 47th days after operation. In the longer survivor the liver was bile-stained and showed intralobular biliary stasis, its parenchyma was not necrotic. In both dogs the grafted kidney was normal macroscopically, and microscopy revealed no evidence of the homograft reaction (fig 2), although there were areas of hæmorrhage in the kidney that functioned for 21 days Both animals were passing concentrated urine up to the time of death. The blood-urea levels are shown in fig 3

In an attempt to prevent the early deaths, the procedure was further modified by performing only unilateral nephrectomy at the time of renal transplantation, leaving removal of the second kidney till a later date

DISCUSSION

In dogs first-stage renal homografts usually cease to function after 4–8 days, showing massive cellular infiltration The longest periods of function in four recent series are 11 days,[2] 12 days,[3] 14 days,[4] and 20 days [5] In an irradiated dog a renal homograft has survived 49 days,[6] and the kidney was found to be normal microscopically

My observations with 6-mercaptopurine suggest that this drug can modify the rejection of renal homografts in dogs It could have advantages over total body irradiation in being less hazardous, and possibly less crippling immunologically, though it seems to increase liability to infection and can cause hepatic biliary stasis [7] Its use might thus offer an approach to renal homografting in man, especially in chronic uræmic patients in whom homograft rejection is already depressed [8]

The effects observed could be explained either by a non-specific cytotoxic action of the drug on the immune system, or by a true specific production of immune tolerance This problem is being investigated

I am much indebted to Prof D Slome for his help and encouragement and to the council of the Royal College of Surgeons for providing facilities, materials and technical assistance at the Buckston Browne Research Farm, where this work was done I am also grateful to Mr J P Hopewell and Dr K A Porter for their guidance and advice

Burroughs Wellcome & Co provided the 6-mercaptopurine, which was prepared for me in the dispensary of the Royal Free Hospital The histological sections were made in the hospital's department of pathology

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R Y Calne
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New Inventions

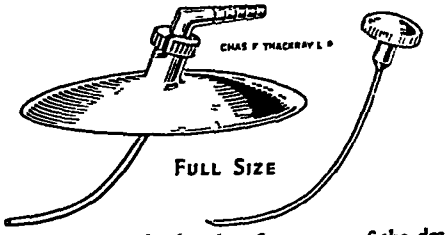
CANNULA FOR TREATMENT OF SUBDURAL EFFUSIONS IN INFANTS BY CONTINUOUS DRAINAGE

Subdural effusion is fairly common in infancy and causes a high morbidity if neglected Early treatment must be undertaken to avoid restriction of brain expansion and to prevent impairment of mental development It is important, therefore, to remove the fluid which collects in the subdural space

When the effusion is a true hæmatoma one or two subdural taps usually suffice But if the effusion is a subdural hygroma, after subdural tap the fluid rapidly collects again from the subarachnoid space, being pumped up by leakage Hence continuous drainage may be necessary to allow adhesive obliteration of the subdural space

The immediate evacuation of large subdural effusions in infants carries a high mortality an early, but gradual, release of pressure is preferable The practice in some clinics is to perform subdural taps daily on alternate sides, removing 10–15 ml of fluid each time If the fontanelle quickly becomes tight again, or, if the baby's general condition is poor, it may be necessary to tap more frequently For many years Prof Norman Dott of Edinburgh has advocated a system of continuous drainage of the subdural space

Continuous drainage avoids the need for multiple punctures —which can lead to infection—and reduces the distress caused to the child and the possibility of bleeding after frequent needling By adjusting the height of pressure of the drainage system the rate of evacuation can be controlled, thus permitting slow progressive drainage over days, and facilitating the adhesive obliteration of the subdural space



With this method of treatment, operative excision of hæmatoma membrane will rarely be needed (Such membrane, composed of fibrin, may form on the undersurface of the dura and become a " space-occupying lesion ")

The requirements of a continuous drainage cannula are

1 It should be of reasonable calibre to permit free drainage without blockage

2 With its attendant fine trochar it should easily enter the subdural space with a clean puncture and negligible trauma

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4 Egdahl R H, Hume, D M *Surg Forum*, 1955, 6, 423
5 de Klerk, J N, Scott, H W, Scott W W *Ann Surg* 1954 140, 711
6 Mannick, J A, Lochte, H L, Ashley, C A, Donnall Thomas, E, Ferrebee, J W *Surgery*, 1959, 46, 821
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1955, 34, 327

3 It should fit snugly and firmly to the scalp with the minimum of dressings Unless it is secure, its movement may cause further bleeding in the subdural space

4 The connection from the cannula to the drainage tube leading to the collecting-flask must be securely locked, loose attachments which are liable to come adrift lead to unsterile attempts at reconnection, with the possibility of infection

The present cannula meets these criteria. The trochar and cannula are made of stainless steel and are size 18 or 19 B W G The cannula is attached to the scalp shield at an angle of 30° This allows it to drain the subdural space while the shield is firmly applied to the scalp The fixity of the shield minimises movement of the cannula, which cannot "wiggle" or "move" inside the skull The connecting link to the cannula is a 'Record' pin locking movement which affords a firm connection and from which the rubber drainage tube leads to a conical half-pint collecting-flask. This flask is held in place at the end of the cot with a double clamp which can be raised or lowered, thus altering the head of pressure and enabling the rate of escape of the effusion to be controlled.

Procedure

The standard procedure for subdural tap in infancy is followed. The crown of the infant's head is carefully shaved and cleansed and held firmly in a sterile towel by an assistant. Professor Dott tells me that he has found the following cleansing technique satisfactory for preventing the infection which may arise with indwelling drainage tubes in the subdural space

"The scalp is washed carefully with cetrimide ('Cetavlon') and rinsed with saline While it is still moist 'Polybactrin' antibiotic spray is applied to the scalp A blob of 'Cicatrin' (antibiotic cream) is applied to the scalp on the site where the cannula puncture is to be made In addition to its valuable antibiotic content the lubrication effect of the cicatrin cream makes for a clean and easy puncture"

A thin gauze dressing 2 or 3 mm larger in diameter than the scalp shield is pierced centrally by the trochar and cannula and slid into position on the under-surface of the shield. The subdural space is then punctured and the trochar is immediately eased back, but it is not withdrawn, lest there should be a sudden uncontrolled release of the subdural effusion. The cannula is then gradually and gently slid into the subdural space, with the shield resting gently and evenly on the scalp The trochar is withdrawn and the connecting-piece is locked in position, having already been connected by the rubber tube to the collecting-flask. The patency of the drainage having been established, the cannula is firmly fixed in position by placing four pieces of $^1/_2$-in. 'Sleek' adhesive a few inches in length across the shield, crosswise, after cleansing the scalp with ether In practice, even if the infant is restless, the cannula is very unlikely to work loose or disconnect, and routine nursing and feeding can be followed without hindrance

The cannula should not be left in any one puncture site longer than three days A few fresh punctures can of course be made, the complete drainage apparatus having been resterilised before reconnection, but the duration of continuous external drainage should be limited to two or three weeks at most. For the very occasional case where fluid is still collecting after three weeks, the extra-light-opening-type of Spitz-Holtzer valve might perhaps be used as a means of closed internal drainage

I am grateful to Prof Norman Dott and to Mr W R Henderson, and also to Mr Lockhart, of Messrs Charles F Thackray & Sons, Leeds, who manufactured the cannula

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Reviews of Books

Human Biochemical Genetics

H HARRIS, M.D, reader in biochemical genetics, London Hospital Medical College London Cambridge University Press 1959 Pp 310 37*s* 6*d*

DURING the past three years there has been a flush of books, articles, and symposia on various aspects of human biochemical genetics This is no more than it should be "From being an obscure subject, supposedly only pursued by academically minded cranks and of little significance in therapeutics, the study of inborn metabolic errors is becoming a very important branch of medicine" so wrote Penrose in 1957 This excellent book, written by one of the leaders in the field, has come at an opportune moment. The literature has been scattered among the biochemical, medical, and genetical journals, so that many doctors have been slow to grasp the enormous impact of this subject on clinical medicine Already, however, many of the larger medical schools, in the admittedly specialist-minded United States, are pondering the establishment of departments of medical genetics

The book begins with an introductory account of the principles of human population genetics Disturbances of aminoacid metabolism, carbohydrate metabolism, human hæmoglobins, blood-group substances, and plasma-proteins are among the subjects discussed informatively They are, moreover, discussed not from the viewpont, too often adopted these days, of metabolic defects which "happen to be inherited" but from the more sophisticated viewpoint of problems in classical biochemical genetics Inevitably the book reflects the author's interests and experience and would not claim to be encyclopædic.

The chapter on the human hæmoglobins is as up to date as possible in a rapidly moving subject. Dr Harris properly lays emphasis on the extraordinary fact that the substitution of a single aminoacid (valine for glutamic acid, for example) in a hæmoglobin molecule consisting of approximately 560 aminoacids can result in the difference between normal and sickle-cell hæmoglobin—between health and disease Unquestionably, many aspects of this section will need to be rewritten and enlarged in future editions The aminoacid sequence in the anomalous peptides of hæmoglobin C and S (illustrated in fig 46) will have to be revised in the light of Ingram's recent work. The details are less important, however, than the general concepts, which are admirably emphasised.

The chapter on blood-group substances is an extremely clear exposition of a difficult subject. The section on inherited serum-proteins, however, is a little sketchy There is no mention of the inherited variation in serum-albumin, first described in 1957, in which serum-albumin is present in two distinct molecular species ("double albumin"), nor indeed of certain other inherited serum-proteins, some of which have been recently described by Dr Harris Unavoidable delays in publication are no doubt largely responsible. The beta-globulin variants are now recognised as transferrins, and the account of inheritance of the gamma-globulin groups will have to be expanded considerably in later editions The current and lively topic of the genetic aspects of antibody formation is not discussed, and surprisingly no reference is made to the contributions of Beadle and Tatum, whose work in biochemical genetics, albeit in species other than man, has been outstanding Dr Harris has remained strictly within his title and some readers would perhaps have liked at least an occasional reference to species other than man

Nowhere are the disciplines of biochemistry and clinical medicine more closely linked than in the conditions discussed here, and we hope this book will reach the desks of all biochemists concerned with the teaching of medical students The author might have permitted himself the luxury of a little more speculation he does not, for instance, discuss in any detail the possible ways in which alteration of the base sequences in D N A. can give rise to altered proteins We find little or no mention of coding mechanisms, soluble R.N.A, or ribosomes, but these are small points Only a few misprints were noticed in a book which successfully combines sound production with modest price.

There is no doubt that this is the best book on human biochemical genetics available today Dr Harris is to be congratulated on a much needed work well done it can be warmly and unreservedly recommended.

Water Supply for Rural Areas and Small Communities

E G WAGNER, chief engineer, division of health and sanitation, Institute of Inter-American Affairs, Rio de Janeiro, J N LANOIX, sanitary engineer, division of environmental sanitation, W H O, Geneva World Health Organisation Monograph Series no 42 Geneva W H O (Obtainable from H M Stationery Office, P O Box 569, London, S E 1) 1959 Pp 340 35*s*

THOSE who first urged a clean water-supply may have been stirred by irrational emotions derived ultimately from J J Rousseau, but they did as much for the public health as all the bacteriologists put together We turn on the tap and accept their bounty without question. To us typhoid and other water-borne infections are no more than rare curiosities Most of the world's inhabitants are, however, still countrymen who lack piped water, main drainage, and electricity—and of these the first is the most important by far One of the happiest pages in the history of our rule in India is the effort made to give the villager a "safe" well, and now almost everywhere clean water has a top priority

This book is a model for what such publications should be It is practical and inclusive and cheap In it anyone from Iceland to Peru can find plain directions for the choice, impounding, and purification of any sort of available water he can get some idea of the cost of building and working the supply and the staff which will be needed The book may emanate from Geneva, but the authors know from personal experience that most wells are still dug with pick and shovel or mattock and the earth removed in a basket on a rope

The book fills a need even in this country Few medical officers of health have had the opportunity to learn much about emergency water-supplies, and circumstances could arise in which these would have to be improvised amid wreckage and confusion.

J M Charcot, 1825-1893

His Life—His Work GEORGES GUILLAIN, M D Edited and translated by PEARCE BAILEY, PH D, M D, director, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland London Pitman Medical Publishing Co 1959 Pp 202 50*s*

THOSE Parisians who lived within the ramparts of the old city during the middle of the sixteenth century were so often disturbed by violent explosions in the royal arsenal that they petitioned Louis XIII to store his gunpowder elsewhere In 1565 he acceded to their request, and erected another arsenal on the opposite bank of the Seine In later years these buildings were much enlarged, and came to be used as an infirmary, at first for destitute women and prostitutes, and then for the chronic sick, the crippled, and the insane At times this "grand asylum of human misery" housed as many as 8000 patients, some under appalling conditions The work of such men as Pinel, Magendie, and Cruveilhier did much to ameliorate and to enhance the reputation of the Salpetriere (as the institution continued to be called) But it was the appointment, in 1862, of Jean Marie Charcot, as its chief of the medical service, which was destined to make it a Mecca of doctors the world over

A modern physician, as Professor Guillain points out, finds it hard to appreciate the debt neurology owes to Charcot When he began his work at the Salpêtrière, scarcely anything was known of the pathology of nervous disease the methods of clinical examination in common use were rudimentary and ineffective and such terms as "tremor" and "paralysis" were regarded as constituting a sufficient diagnosis in themselves One half of this book describes in considerable detail the publications and researches by which Charcot raised the whole status of our knowledge of diseases of the central nervous system the other is devoted to a personal biography Though its author never met Charcot, he is senior enough to have known many of his pupils and friends, and his book is an important contribution to our knowledge of a man who has not hitherto received from biographers the attention he deserves, as the Father of Neurology

Recent Progress in Psychiatry

Vol 3 Editors G W T H FLEMING and A WALK London J & A Churchill 1959 Pp 397 42*s*

THIS volume is the third in the deservedly well-known series sponsored by the Royal Medico-Psychological Association (others appeared in 1944 and 1950) and the contributions live up to a distinguished tradition Since many relevant advances have been made in related disciplines, clinical chapters are rather fewer, and the condensation of a vast area (nearly 2000 references are covered) makes for hard reading in places, although Prof Alexander Kennedy and Dr F J Fish, for example, writing on addiction, and Dr R. Gibson on mental deficiency, show that brief but extensive surveys can be both scholarly and easy to read Other topics authoritatively covered are surgical treatment (Mr M. A Falconer and Mr Peter Schurr), child psychiatry (Dr Kenneth Cameron), major crime (Dr Jonathan Gould), and genetics (Dr Valerie Cowie and Dr Eliot Slater) More abstruse are biochemistry (Dr Derek Richter), enzymes (Dr Gould), the physiology and pathology of cerebral structures (Dr T P S Powell, Dr J A N Corsellis, Dr Alfred Meyer, Dr R M Norman, and Dr Henry Urich), cybernetics (Dr W Ross Ashby), and personality testing (Prof H J Eysenck) A name index, an ampler subject index, and prompter publication (the most recent papers quoted are 1956) might be possible for the next volume

In his introduction Dr Fleming declares

> "*Modern psychiatry is passing through a period of apparent* change The law relating to mental illness has come under considerable criticism, some of it from the unstable and hysterical *This has* led to changes in administrative outlook which are certainly not always in the best interests of the patient, his relatives, or the public, but bolster up the ego of the inferiority unconscious psychiatrist. Amongst the inexperienced there is an impression that what they *are doing has never been done before, and they* either make no attempt to ascertain how much was done twenty and more years ago, or turn a *deaf* ear and a blind eye"

If one of the objects of this sharp passage is to restrain over-enthusiastic zeal for reform it should surely have been more sympathetically worded As it stands it can hardly fail to sour the atmosphere what is needed by young and inexperienced enthusiasts (of whom there seem to be too few by our reckoning) is guidance and encouragement

Fundamentals of Gynecology

SAMUEL J BEHRMAN, M S, M R C O G, F A C S, associate professor, obstetrics and gynecology, University of Michigan Medical School, JOHN R G GOSLING, M D, assistant professor, obstetrics and gynecology, University of Michigan Medical School New York and London *Oxford University Press 1959 Pp 416 76s*

THIS new book by two American teachers is based on the lecture course in gynæcology at the University of Michigan Medical School and is designed for senior students and general practitioners It gives a lucid, well-ordered account of modern gynæcology, in which the British viewpoint is well represented The general layout of the material is sound and the exposition clear The publishers deserve special credit for the excellent production

Each chapter is a short, balanced, and authoritative monograph on some division of gynæcology At the end of every chapter there are appropriate references, British and American, to which the reader may turn for more detailed information. The chapters on Virilism and Intersexuality in the Female, Endometriosis, and Hydatidiform Mole and Choriocarcinoma are especially valuable, and the whole section on malignant disease is very effective, though conceivably it might be improved by more detail about the place of cytology in the early diagnosis of cancer of the cervix The text is well illustrated by diagrams, photographs, and drawings, but occasionally the photomicrographs are too small for detail to be seen.

THE LANCET
LONDON 20 FEBRUARY 1960

The Report

THE Royal Commission remark ruefully that their task was expected to be simple but proved otherwise Though they have listened patiently to a great many suggestions for improving the National Health Service, they have had to resist any temptation to solve all its problems But their recommendations, though mainly monetary, reflect well-founded and friendly opinions, on the profession and the service, for which we can be thankful.

Some things that people told them, they do not accept they are not bothered about medical emigration, for instance, or a decline, so far, in recruitment They flatly declare, too, that remuneration can no longer be governed by the Spens reports As basis for their own conclusions they have collected a mass of new information about medical and other incomes, from which they conclude that medical earnings are too low But they also add opinions which reflect their experience in other branches of life—notably that the young doctor is relatively underpaid, that the range of incomes should be wider, and that special distinction—in general practitioners as well as in consultants—needs financial recognition. Promotion and differential remuneration are never quite equitable, in any organisation, but on the whole the system works The Commission find it hard to believe that Medicine alone has a complete lack of "that selective ability which is exercised in practically all other occupations" Not without humour, they suggest that their proposed fund of £500,000 a year, set aside for recognising distinguished general practice, shall revert to the Exchequer if not used

For consultants, distinction awards should, they think, be higher but limited in number, and substantial rises of pay are proposed for all hospital staff Leaving to the Platt Working Party the question of hospital grades, the Commission do little to solve the registrar problem except that they leave senior registrars on a rising scale for a longer time Their most important change of relativities lies in the higher pay for registrars, senior house-officers, and particularly house-officers, who "have been greatly underpaid both in relation to their seniors and in relation to what is paid to comparable people in other professions" Whereas elsewhere the Commission's rates are a little lower than those suggested by the British Medical Association, for the house-officer they are higher Another recommendation designed to help peripheral hospitals would entitle these to pay an additional £100 a year to junior staff

The Commission's proposals for general practice are preceded by a masterly review of the practitioner's present situation. They would retain capitation fees, and the pool; and, though the amount to be put into this for each doctor would be raised only to £2425, they say that, with changed methods of calculating the pool, this would mean an average increase of £450 over 1955–56 Professor JEWKES, in an impressive memorandum of dissent, argues that this increase, like that suggested for part-time consultants, is too low either to restore confidence or to ensure recruitment he says that unless practitioners' remuneration is now raised by at least 30% over that ruling in 1955–56, their position will have deteriorated during the decade in relation to that of other people On reduction of the maximum list the Commission do not commit themselves whatever is decided about this, they are anxious that a wide range of incomes shall be achieved—the distinction award being one possible means "We do not believe that constant striving for increased income is or should be the main incentive to good general practice, but at the same time we think it must be discouraging both to existing doctors and to potential recruits if a really first-rate practitioner has so little prospect of earning more than one who is merely satisfactory" Again urging better pay for the young, they are generous to the trainee assistant. Other assistants, they hope, will benefit too, though less directly

Even more important than what is paid in 1960-63 is what happens later We are all painfully familiar now with the type of Government economy which asks disproportionate sacrifice from people who happen to be paid from public funds, and we are grateful both for the Commission's acid statement that "doctors and dentists must have some confidence that their remuneration will be settled on a just basis" and for their declaration that "doctors and dentists in the public service should not be used as a regulator of the national economy" To review major issues periodically, the Commission propose a standing Review Body, of seven independent persons, to advise the Prime Minister (Professor JEWKES, who evidently shares our wish for more strategic planning of the Health Service, would like to see this develop into an Advisory Council) The Commission remark, again rather pointedly, that the recommendations of the Review Body "must only very rarely and for most obviously compelling reasons be rejected" Their request that £11 million shall now be paid to general practitioners, and £9 million to hospital doctors and dentists, in respect of the time elapsed since the inquiry began in 1957 is evidence that they do not regard the profession's repeated protests as baseless We earnestly share their hope for an end, once for all, to the damaging disputes of the past.

Hæmorrhoids

"NATURE is not infallible," Saki's major observed, "but she usually abides by her mistakes" Whether they are inborn flaws or signs of imperfect adaptation, a host of minor ailments that beset us after the age of twenty seem to support his contention Hernias, varicose veins, slipped discs—all carry an excellent prognosis for life and a tolerable one for comfort, but the chances of complete cure are often remote By most published accounts hæmorrhoids—perhaps the most important member of this group—are the exception, for they are said to be eminently curable But are they in fact? The truth about hæmorrhoids is not easily discovered to many doctors they remain an unexciting and to most patients a faintly embarrassing complaint And yet these patients form a large proportion of chronic bleeders, and chronic bleeders, with their lowgrade but intractable iron-deficiency, should be one of our pressing concerns Neither ill nor well, unable to cope with their work and incapable of enjoying their leisure, these men and women become, in the prime of their lives, a trial to themselves and an unrecognised burden on the community They also become the worst of patients—truculent in seeking advice, erratic in following it, always ready to take their own discharge once in hospital It is hardly surprising that many are fobbed off by their doctors with iron—any old iron—at an early stage of their illness and thus find themselves launched on a vicious circle of bleeding, iron-deficiency, increasing istrogenic constipation, more bleeding, and worse iron deficiency Even spontaneous remissions are not an unmixed blessing, for they promote indiscriminate claims made for a bewildering variety of patent "anti-hæmorrhoidals"—some so extravagant that they could hardly be expected to sell were prospective buyers' critical faculties not blunted by a hæmoglobin of 60%

The rational management of hæmorrhoids, like that of most common but not life-threatening illnesses, calls for a compromise between the ideal and the workable To preach prophylaxis, tracing back the condition to bad bowel-habits inculcated in childhood, is hardly practical, nor is it realistic to suggest (as some textbooks do) that every case of rectal bleeding should be investigated not only clinically but also hæmatologically and radiologically Isolated episodes in young people are extremely common and usually of no significance intelligent assessment of the history and a brief general and careful rectal examination is all that they require If the bleeding recurs, however—and before embarking on surgical treatment—at least two common underlying causes must be excluded The spectre of hæmorrhoids masking carcinoma of the rectum so effectively haunts most newly qualified doctors that their elders are more likely to offend Less widely appreciated is the common association between non-specific proctitis (with or without hæmorrhoids) and rectal bleeding, and, even when remembered, the diagnosis may tax the most experienced

When a serious underlying disease has been excluded, a course of injections can be confidently recommended for grade-1, grade-2, and even some grade-3 hæmorrhoids—provided that emphasis is laid on the "course" Proctologists often deplore that the average patient, delighted by even a temporary respite, is not urged by his general practitioner to attend a second and third time, but proctologists themselves are not entirely blameless In skill, hygiene, and efficiency the special clinics which are now run by most hospitals have been a great advance on the old system of seeing rectal cases in general surgical outpatients, but all too often increasing efficiency generates an unwholesome conveyor-belt spirit Clad in gaily coloured but ill-fitting dressing-gowns patients are marched by sister into grim little cubicles, instructed to hop on a couch, and reduced into a position which can demoralise the toughest, and after an anxious wait (which might have served as RODIN's inspiration for his *Danaïde*) they may find themselves impaled on a sigmoidoscope without having set eyes on the surgeon Inflated, injected, and thoroughly intimidated, most of them are yet grateful for the relief afforded by the treatment, but their disinclination to attend again is not perhaps to be wondered at Serious complications from injections are oddly few potentially perhaps the gravest, as also the most insidious, is hepatitis from intravenous phenol

For hæmorrhoids which recur after two or three courses of injections and for most grade-3 cases well-conducted hæmorrhoidectomy is thoroughly worth while, but what a "well-conducted hæmorrhoidectomy" means has been disputed almost since the dawn of surgery The results from the clamp-and-cautery operation, as described by FARQUHARSON,[1] and from the St Mark's Hospital dissection-ligature operation[2] have been compared by CORMIE and MCNAIR[3], and their findings shed light on the late results of surgical treatment in general 163 consecutive patients who had been treated in one unit of the Edinburgh Royal Infirmary by one of the two operations were circularised by letter and 100 were available for reassessment After an average of four and a half years only 65 could be classified as "excellent" results, but the criteria were strict, and "no less than 94 of the 100 patients were either cured or were improved to the degree of suffering from only minor occasional symptoms All these patients were in no doubt about the merits of the operative treatment and many expressed the wish that they had come at an earlier date and so saved themselves many years of discomfort" On the other hand, it is perhaps not unreasonable to assume that (apart from 10 who had died from other illnesses since the operation) the 53 who could not be traced or who could not attend may have included a larger proportion of dissatisfied patients, nor would a five-year follow-up include late recurrences Immediate complications were few after either operation only 1 patient had a hæmorrhage, and this *responded to conservative* measures

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[1] Farquharson E L Textbook of Operative Surgery Edinburgh, 1954

[2] Milligan E T C Morgan, N C, Jones, L E, Officer, R *Lancet* 1937, ii 1119

[3] Cormie, J, McNair, T J *Scot med J* 1959, 4 571

(Hughes[4] reported 3 cases of this, potentially the most serious, complication in a series of 221 cases) Postoperative retention, regarded by some as almost inevitable, was rare in both groups, but pain and discomfort were strikingly less after the clamp-and-cautery procedure Cormie and McNair recognise that this may reflect small individual differences in technique (such as the use of a flatus tube instead of petrolatum-jelly on soft dressings), but conceivably the linear scars of the cautery are in themselves less painful than the raw surfaces left after dissection and ligature Of the late complications stricture-formation is the one most dreaded, and, especially when not recognised in time, it can indeed be a disaster In the Edinburgh series mild stenosis was slightly commoner after the St. Marks' Hospital procedure, but such stenosis can follow any operation (and even misplaced injections) and probably results from some error in technique The need for a "tidy" end-result is doubtful skin-tags are usually symptomless but commoner when the cautery has been used Chronic fissure-in-ano—a far more troublesome sequel—appears to have developed in about the same proportion of the two groups

What emerges from the Edinburgh and similar surveys is that, good though the results are, there is scope for improvement at all stages of the illness and all levels of its management. Hæmorrhoids are said to have been one of the three essential adjuncts and afflictions of the successful Victorian physician A paunch was his hallmark of well-merited affluence, baldness gave him an air of experience and wisdom, and hæmorrhoids ensured a look of constant anxiety We can pride ourselves of having shed both the substance and the meaning of the first, we are casting doubt on the interpretation of the second, but we remain faithful to the third Hæmorrhoids is still a disease of the professional classes it deserves the interest—but is often accorded the neglect—of a doctors' ailment.

Fifteen Years of Antibiotics

In 1945 the only antibiotic available for systemic use was penicillin today there are about fifteen How then do we stand? So wide a question demands a comprehensive answer, and we are fortunate that this has been given in a valuable issue of the *British Medical Bulletin*,[5] edited by Prof L P Garrod, which contains fifteen articles by eighteen other experts If all users of antibiotics read and understood these articles there would surely be a great increase in the efficacy of antibiotic treatment combined with a striking reduction in the number of patients given antibiotics, the number of undesirable complications, and the number of antibiotic-resistant strains of bacteria It is not possible for anyone—or any Government agency—to utter a series of commandments on the use of antibiotics, because there are important aspects of the subject about which it is not yet possible to dogmatise But clearly an antibiotic is often given without a clear enough reason in the mind of the doctor prescribing it True, what begins as a minor illness not apparently requiring an antibiotic may develop into something more if it is not treated, whereas it may respond admirably if it is treated As Garrod and Scowen[6] say "Each case must be judged on its merits, but if these are deliberately assessed, and if the treatment has an explicit rational basis, really indiscriminate use will thereby be excluded "

Clinicians are not slow to emphasise that they know of cases in which a laboratory report on the sensitivity or resistance of an organism to a particular antibiotic did not correlate well with the patient's response to treatment with that drug This observation is often enough correct, and there are at least seven possible explanations for it (1) an effective antibiotic may be unable to reach a sensitive organism (in dead tissue or pus, for example), (2) if infection is secondary to obstruction or stasis, in the urinary tract or elsewhere, the effect of any chemotherapy will be only temporary unless the underlying condition can also be relieved, (3) special conditions may be needed for an antibiotic to act (streptomycin, for example, is about 50 times more active in an alkaline than in an acid urine, whereas penicillin and chlortetracycline are more effective in an acid medium), (4) the antibiotic may be diluted beyond the point of effectiveness (a mischance especially probable in urinary infections because these patients are traditionally urged to drink all they can, whereas restriction of fluids for a time is necessary to secure the greatest possible concentration of the drug in the urine), (5) resistance of an organism to a particular antibiotic, reported by the laboratory, does not hinder natural recovery from an infection which would resolve without chemotherapy, (6) the sensitivity of the culture tested in the laboratory may differ from that of the organism in the patient's tissues, and (7) circumstances may sometimes allow the attainment of concentrations of antibiotic in the tissues greater than those normally to be expected Despite discrepancies of this kind, Gould[7] leaves no doubt about the important part which the laboratory should play in assisting chemotherapy, for clinical diagnosis is not often a dependable guide to the identity and antibiotic sensitivity of the infecting organisms Further, the laboratory may help in measuring the efficacy of treatment and aid the clinician in his decision when he may safely stop it.

Lowbury,[8] discussing possible measures to combat the emergence of drug-resistant pathogens, evaluates discriminating restraint in the use of antibiotics, prevention of hospital infection, well-chosen combinations of drugs for a few special infections, and agreed schemes for the use of antibiotics in rotation—a change being made as soon as, or preferably before, drug-resistant strains of bacteria appear He rates attempts to prevent cross-infection as probably the most important, but finds better hopes in some of the newer antibiotics than seemed at all likely a few years ago Some of these new drugs are too toxic for parenteral use, but others are not

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[4] Hughes, E S R Surgery of the Anus, Anal Canal and Rectum Edinburgh, 1957

[5] Antibiotics in Medicine *Brit med Bull* 1960 16, 1–85

[6] Garrod, L P, Scowen E F *ibid* p 23

[7] Gould J C *ibid* p 29

[8] Lowbury E J L *ibid* p 73

—although, in general, the treatment must be conducted with a sharp watch for toxic signs and a resolve not to overdose the patient or unnecessarily prolong the treatment Usually combinations of drugs are needed for the treatment of tuberculosis and subacute bacterial endocarditis caused by enterococci **Barber** et al[9] showed that the combination of novobiocin and erythromycin apparently prevented the emergence of resistant strains, whereas the combination of chloramphenicol and erythromycin should be avoided because of cross-resistance between the two drugs Obviously, the use of antibiotics in combination requires much more critical thought and study than it has yet received It is a relief that the uncritical enthusiasm for combinations which was notable a few years ago appears to have abated

The enterprise of those who have pioneered the development of antibiotics has been notably supplemented, to the benefit of all, by the outstanding efforts of the pharmaceutical industry Understandably the industry wishes to have a reasonable financial return, but probably all of us, including the industry, would be happier if the over-enthusiastic reports of uncritical users of some of the new preparations were carefully, realistically, and even sceptically assessed before they were allowed to exert any great influence on sales policy

Annotations

ESCHERICHIA COLI IN PETS

A few weeks ago we called attention to the dangers of keeping dogs, and indeed of having anything at all to do with them[10] Now a further possible hazard has been revealed Mian,[11] working in Michigan, examined 321 household pets and found serotypes of *Escherichia coli* known to be associated with infantile enteritis in 14% of dogs and 8% of cats Furthermore in one instance he detected the same serotype (O 55 B5) in a child with diarrhœa and in a dog in the same house (the possibility that the baby infected the dog does not seem to have been considered)

Knowing the almost indecent intimacy which many pet-lovers allow their furry friends, we are not surprised, and yet we feel bound to accept this warning with some caution There is no longer any doubt that certain serotypes of *Esch coli* cause enteritis in children under 2 years and occasionally in older people, but the same serotypes are also found not uncommonly in apparently healthy persons of all ages No-one has brought forward very convincing evidence that babies are infected by their mothers or vice versa "Scouring" in calves deprived of maternal colostrum is also caused by certain serotypes of *Esch coli* Some of these are identical with those implicated in human disease, and it was thought at one time that cow's milk was an important source of human infection In recent years, however, the serotypes prevalent in calves and babies have not been the same, and indeed one of the most interesting things about these diseases is the changes over the years in the types most commonly associated with human and bovine disease In this country types O 55 and O 111 have largely given way to O 26 and O 119 in babies, while in calves O 78 and O 137 have displaced O 9, O 26, and O 35 Other serotypes—some shared with humans and calves—have been found to cause enteritis in lambs and various ailments in piglets[12] It is a reasonable guess that all young animals are liable to these infections, but whether the disease in one species has any relation to that in another we do not yet know Incidentally some of these pathogenic serotypes have been found in well-water

This epidemiological problem is confusing Interest in the enteroviruses has encouraged the idea that enteric disease in the young is due to one or more viruses an that the "pathogenic" serotypes of *Esch coli* are norma inhabitants of the upper bowel flushed down by vira diarrhœa (In current medical conversation "viru infection" is likely to mean "a disease of uncertai ætiology") Yet recognisable enteroviruses are rarely i ever found in patients with diarrhœa who are excretin any of the specific serotypes of *Esch coli*[13] For th moment we must accept that these are the cause of th *disease, and, yet clearly the epidemiology of "col enteritis"* differs quantitatively if not qualitatively from *such infections as typhoid fever or Sonne dysentery* The number of symptomless excreters—"carriers" begs too many questions—is far greater, and yet when the disease spreads in a children's ward it is highly infectious and persistent In some well-run hospitals the disease is almost always present in others, a few miles away, only occasional sporadic cases are seen

We hope that others will repeat Mian's work and compare their findings with those of the local hospital The origin of single infections is always obscure, and domestic pets are as likely a source as any It is true that not much has come of the observation that about 3% of dogs carry *Salmonella spp*, but perhaps this lead has not been pursued with enough vigour At any rate these findings give the family doctor yet another reason to discourage dogs from sleeping on beds or licking the baby

AUTOMATION

Automation—a threat to the community or a panacea? Whatever its advantages it clearly raises problems, including problems of mental health, and W H O has published the report of a study group which considered this aspect[14] The study group point out that automation may be broken down into three overlapping types "transfer automation" of the assembly-line type now long familiar, "control automation" based on automatic feedback of information into a mechanical system, and "computer automation", the most revolutionary, used most commonly in the recording, coordination, and analysis of information for administrative purposes Automated work may affect the functioning of operators, and therefore possibly cause mental ill health, through increased responsibility without action to provide relief, through the need for close attention without adequate motor discharge, through solitariness, and through "depersonalisation" The need to react almost instantaneously to alarm signals is a particular strain, which may be alleviated by rational grouping of indicators and the presentation of useful information only Adequate changes of position and good general environmental conditions are also important The effects of excessive isolation and absence of social contact are compared with

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[9] Barber, M Csillag A, Medway, A J *Brit med J* 1958, ii, 1377

[10] *Lancet* 1959 ii, 1017

[11] Mian K A *J Amer med Ass* 1959 171, 1957

[12] Rees, T A *J comp Path* 1958, 68, 388, 399 *ibid* 1959, 69 334

[13] Young V M Warren, J, Lindbergh R B *Proc Soc exp Biol, N Y* 1959, 100, 579

[14] Mental Health Problems of Automation *Wld Hlth Org tech Rep Ser* 1959 no 183 Obtainable from H M Stationery Office, P O Box 569 London, S E 1 Pp 30 *1s 9d*

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PUBLISHED by the PROPRIETORS, THE LANCET LIMITED, 7, Adam Street, Adelphi, in the County of London
Printed by HAZELL, WATSON & VINEY LTD , Slough and Aylesbury—Saturday, October 8, 1960
PRINTED IN GREAT BRITAIN—Entered as Second Class at the New York, U S A , Office.

Special Articles

REMUNERATION OF DOCTORS AND DENTISTS

Royal Commission's Report

THE Royal Commission on Doctors' and Dentists' Remuneration was appointed in 1957 with Sir Harry Pilkington as chairman. Its report, signed by all but one of its members, has been issued this week[1] The commission finds that the present remuneration of doctors is inadequate, and it proposes the establishment of machinery to keep remuneration under review

The commission was appointed to consider

1 How the levels of professional remuneration from all sources now received by doctors and dentists taking any part in the National Health Service compare with the remuneration received by members of other professions, by other members of the medical and dental professions, and by people engaged in connected occupations,

2 What, in the light of the foregoing, should be the proper current levels of remuneration of such doctors and dentists by the National Health Service,

3 Whether, and if so what, arrangements should be made to keep that remuneration under review,

and to make recommendations

GENERAL OBSERVATIONS

The report opens with five important general observations

1 There has been no accurate knowledge of the level and spread of earnings in the medical and dental professions, nor of how their earnings compared with those of other people of broadly similar attainments

2 There has been no attempt to ensure that the recommendations of the Spens Committee accepted by the medical profession and the Government as to the spread of earnings among general medical practitioners were carried out.

3 There has been a complete absence of any effective machinery to see that dentists earned what had been intended, as a result they have earned more

4 Owing to the shortage of dentists, general dental practitioners have worked longer hours and have earned more than was envisaged by the Spens Committee, and more than general medical practitioners

5 The uniformity of pay scales in the hospital service has not taken account of the wide variation in attractiveness to the young doctors of the various types of hospital

The commission declares "We reject the suggestion that doctors' and dentists' pay can be settled by the application of a formula, tied to the cost of living, or to a special index", and it recommends the setting up of a review body, somewhat similar to the Advisory Committee on the Higher Civil Service, to watch the levels and spread of medical and dental remuneration, and to make recommendations to the Prime Minister

"The main task of this Body will be the exercise of the faculty of good judgment, and it must be composed of individuals whose standing and reputation will command the confidence of the professions, the Government, and the public. It must be regarded as a better judge than either the Government or the representatives of the professions as to what the levels and spread of medical and dental remuneration should be

"While the Government cannot abrogate its functions and responsibility for ultimate decisions, we are insistent that the recommendations of the Review Body must only very rarely and for most obviously compelling reasons be rejected"

The commission attaches great importance to prompt action by the Government in dealing with the review body's recommendations "Nothing will restore confidence between the professions and the Government more than experience of really prompt action on the recommendations of the Review Body"

The commission declares that, now that the vast majority of their earnings come from the State—"a monopoly employer for practical purposes"—doctors and dentists should have their remuneration settled by external comparison, principally, though not necessarily exclusively, with professional men and others with a university background in other walks of life

In deciding where doctors and dentists should stand in relation to members of other professions, regard should be paid among other matters to the general trend of recruitment in quality and quantity, and to the relative status of the medical and dental professions and of other occupations in other countries But earnings should not be determined by short-term supply and demand In common with the Willink Committee, the commission does not propose that attempts be made to alter the level of recruitment by adjusting remuneration

The report suggests that to supply the review body with the necessary information, the Government must procure a continuous flow of classified statistics showing the level and spread of earnings among doctors and dentists and all who may be regarded as comparable, and this information can most simply and reliably be obtained from the Inland Revenue, with safeguards against identification of individuals or small groups

As regards dentists the commission views "with disfavour the failure of the profession and of the Government to establish a method that would ensure that dental earnings match intentions

"Since earnings continue to rise we recommend that no changes in current payments for items of dental service should take place until effective machinery is working to ensure that intentions as to levels of earnings are fulfilled

"We accordingly recommend that a permanent study group should assess and keep under review rates for items of service based on proved performance of dentists It will be for the Review Body to say what dentists in the future ought to earn, it will be for the study group to arrange that this is what they do earn"

Doctors and dentists in the public service, the report continues, should not be used as a regulator of the national economy Their earnings should not be prevented from rising because of a fear that others might follow

"This does not mean that we consider that either doctors or dentists should ever have a fixed place in a changing world. Over the years, in this country and in others, the financial position held by doctors or dentists may rise in relation to some and fall in relation to others, and in relation to each other, for various reasons including the maintenance of a proper balance of recruitment between these and other professions"

Routine matters of pay adjustments and of general conditions of service should be settled by existing methods of negotiation, whether direct or by a Whitley committee

The commission gave special consideration to doctors in their preregistration year and first few years of registered practice

"Today many young science graduates start earning salaries in the early twenties and in many professions earnings are quite substantial well before age thirty In the light of this, the total earnings of doctors up to age thirty are too low, and we are recommending substantial increases for junior hospital appointments and for trainee assistants, we expect these to affect the salaries paid by general medical practitioners to their assistants "

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[1] Royal Commission on Doctors' and Dentists' Remuneration 1957–60 Cmnd. 939 H M Stationery Office 1960 Pp 346 15s

EVIDENCE ABOUT REMUNERATION

The commission quickly realised that to obtain information about earnings in the medical, dental, and other professions it would " have to embark upon a good deal of original research ", and this it painstakingly did

It has eliminated from all its statistics doctors, dentists, and others (except university teachers) not working full-time The commission concentrated on those aged 30–65, but it remarks that the figures should be interpreted cautiously, as they are affected by the age structures of the samples Furthermore, the figures of income returned by general medical and dental practitioners and by fee-earners in other professions included depreciation allowances on capital outlays (In the case of general medical practitioners these were shown by an expenses inquiry to have averaged £128 in 1955–56, while in the case of general dental practitioners the commission's survey disclosed a figure of £102) Again, the earnings of general practitioners represent the amounts actually received by them in 1955–56, and take no account of arrears

In 1955–56 median earnings in all ages (including those under 30 and over 65), and in those aged 30–65, and estimated total earnings at ages 30–65 were as follows

	Median earnings		*Total*
	All ages *	*Aged 30–65 yr* *	*earnings 30–65 yr* †
Medical ‡			
General medical practitioners	2058	2160	79,000
Consultants	3100	3130	117,000
Senior hospital medical officers	1822	1850	73,000
General medical service		2100	76,000
Hospital doctors		2700	100,000
All N H S doctors		2300	84,000
Dental ‡			
General dental practitioners	2127	2190	79,000
General dental service		2150	78,000
Others			
Accountants	1350	1490	71,000
Actuaries	1940	2020	105,000
Barristers (England and Wales)	1185	1620	92,000
Advocates (Scotland)	1494		72,000
Solicitors (England and Wales)	1750	1850	88,000
Solicitors (Scotland)	1434	1580	67,000
Architects	984	1080	54,000
Surveyors	1146	1360	63,000
Engineers	1181	1210	59,000
University teachers‡	1380	1510	63,000
Graduates in industry	1260	1570	84,000

* No deductions have been made to allow for depreciation, nor, in the case of general medical practitioners, have any additions been made to allow for uneven distribution of pool balances

† These figures are arrived at by taking the average earnings of each age-group, multiplying them by the number of years in the group (five or ten), and adding them all together This device greatly diminishes the influence of temporary differences in age distribution, and takes account of the fact that some professions are most remunerative at one age and some at another The career earnings may be said roughly to represent what a man in each profession who was 30 in 1955 might then reasonably have expected to earn if he worked on a full-time basis until age 65, provided all the circumstances of 1955 remained unchanged

‡ Men only

ASSESSMENT OF EVIDENCE

THE commission remarks that the relationship between earnings in different professions is determined not only by considerations of precise justice and logic, but also by tradition and economic pressures of various kinds Moreover, since increases in professional remuneration are often made at long intervals, in some professions a substantial change may have taken place shortly after the period in which its remuneration was studied Nevertheless, a broad picture can be seen

The Willink Committee, reporting in 1957, suggested that " the reduction of the student intake by about a tenth from as early a date as is practicable would meet the case " The commission found that, whether or not as a direct result of the committee s recommendations, the intake of medical students fell from 2564 in 1957–58 to 2501 in the following year " We are informed that at present all the medical training places can be filled with suitable candidates, but there is no longer the flood of applications that was characteristic of the immediate post-war period The broad conclusions seem to be that the supply of candidates for training as doctors is reasonably close to requirements, and the question of using remuneration as an instrument either for encouraging a greater flow of potential doctors, or reducing the present flow, does not arise "

As regards dentists, since all available places in the schools are now well occupied, it would be pointless to use remuneration as a means of obtaining more potential dentists On the other hand " The level and quality of recruitment to the medical and dental professions may be affected by our recommendations, or the information we publish about the earnings in other professions Any such changes in the level or quality of recruitment would be matters for consideration when medical or dental remuneration is reviewed in future "

The professions, says the report, in giving evidence to the commission laid great emphasis on what was sometimes called " proper implementation of the Spens Reports "

> " We have studied all three reports with great care, but while fully acknowledging the valuable work done by the Committees in providing a basis on which the remuneration of doctors and dentists could at that time be established, we state emphatically that the remuneration of two great professions in the National Health Service can no longer be governed by their recommendations "

The commission acknowledges that its recommendations may lead to repercussions in other fields,

> " and that other groups, some paid from public funds, may argue that implementation of our recommendations for doctors and dentists in the National Health Service ought to be accompanied or followed by increases in their own remuneration
>
> it would be quite wrong for us to revise our recommendations for fear of the cost of possible repercussions "

The commission adds that if, after new levels of remuneration are introduced for doctors and dentists in the N H S , any other doctors and dentists obtain consequential increases in their remuneration, it would also be quite wrong to use these as arguments for further increasing the remuneration of the N H S doctors and dentists

The commission reached five main conclusions

1 At the time of its appointment current earnings of doctors and of dentists were too low

2 Since 1957 earnings in other professions and in industry and commerce at levels comparable with those of doctors and dentists have increased, by rather less than those of general dental practitioners, but by rather more than those of doctors generally and of dentists in the hospital service

3 The commission should recommend levels of remuneration to apply from Jan 1, 1960 Since, however, it was asked to recommend current earnings in 1957 at the time of its appointment, there should be some payment to general medical (but not dental) practitioners and to doctors and dentists in the hospital service to cover the intervening period There should be no retrospective payment for any period prior to the commission's appointment

4 Within the medical profession the overall relationship in earnings between the two branches—the hospital service and general practice—should be broadly maintained unchanged

5 The young doctor under 30 years of age has been underpaid to a relatively greater extent than older doctors, but the young dentist has not been underpaid in relation to the older dentist

" After careful consideration of all the factors we have decided that in 1957 average earnings of both doctors and dentists for the whole career period between ages 30 and 65 should have been about £7000 more than they actually were in 1955/56, and that by 1st January 1960 they should have increased by a further 12 per cent This would give average ' career earnings ' from January 1960 of about £102,000 for the National Health Service doctor and of about £96,000 for general dental practitioners We have also decided that as from 1st January 1960 the younger doctors should receive rather higher percentage increases "

HOSPITAL AND SPECIALIST SERVICES

The suggested new scales of salaries are set out in the accompanying table

Consultants

The commission recommends that as from Jan. 1, 1960, the scale for whole-time consultants should be £2550 at age 34 or on appointment later × £150 (8)–£3750, then after a second year at £3750 one further increment of £150–£3900 The commission has lengthened the scale slightly in order that consultants can look forward to increasing remuneration for a rather longer period than in the past.

The commission is not persuaded by the arguments in favour of weighting, but it admits that its immediate abolition would alter the relativities between whole-time and part-time consultants more than seems justified at present. It therefore recommends retention of a limited amount of weighting on the remuneration of part-time consultants in post on Dec 31, 1959, and on that of certain others

No change is recommended in the circumstances in which payment is made for domiciliary visits

Of distinction awards the commission says

" For our part, we agree that some considerable differentiation of income among consultants is necessary in order that good work may be encouraged and rewarded and that there may be a spread of income among consultants comparable to that in other professions Two common methods of securing differentiation in other fields are not open to the consultant so far as his Health Service work is concerned Unlike some professional men in private practice he cannot vary his fees in accordance with his professional standing, and unlike the salaried employee in most fields he cannot look forward to promotion. In these circumstances we consider the awards system is a practical and imaginative way of securing a reasonable differentiation of income and providing relatively high

PAST, CURRENT, AND RECOMMENDED SCALES

Grade (1)	Scales payable when Royal Commission was appointed. (2)	Current scales (i.e, column (2) plus two interim increases) (3)	Scales proposed by British Medical Association in 1957 figures * (4)	Recommended scales as from Jan 1, 1960 (5)
Consultants (*a*) Basic scale	£1800 at age 30 or less £1950 at age 31 £2100 at age 32 or over × £125 (8)–£3100	£1965 12*s* at age 30 or less £2129 8*s* at age 31 £2293 4*s* at age 32 or over × £136 10*s* (8)–£3385 4*s*	At age 32 the scale to be £2700 × £162 10*s* (8)–£4000 *	£2550 at age 34 or on appointment later × £150 (8)–£3750, then after a second year at £3750 one further increment of £150–£3900
(*b*) Distinction awards	A awards—£2500 (to 4% of all consultants) B awards—£1500 (to 10% of all consultants) C awards—£500 (to 20% of all consultants) (The basic scale of consultants with A and B awards is abated by £300 and £200 respectively)	As in column (2)	A awards—£4000 (to 4% of all consultants) B awards—£2400 (to 10% of all consultants) C awards £800 (to 20% of all consultants)	100 A Plus awards of £4000 300 A awards of £3000 800 B awards of £1750 1600 C awards of £750
Senior hospital medical and dental officers	£1475 at age 30 or less £1525 at age 31 £1575 at age 32 or over × £50 (9)–£2025	£1610 14*s* at age 30 or less £1665 6*s* at age 31 £1719 18*s* at age 32 or over × £54 12*s* (9)–£2211 6*s*	At age 32 the scale to be £2160 × £130 (8)–£3200	£2000 at age 34 or on appointment later × £75 (4)–£2300, thereafter increments of £100 every second year–£2700
Senior registrars	£1100 in the first year £1200 in the second year £1300 in the third year £1400 in the fourth and any subsequent years	£1258 8*s* in the first year £1372 16*s* in the second year £1487 4*s* in the third year £1601 12*s* in the fourth and any subsequent years	£1620 in the first year £1800 in the second year £1980 in the third year £2160 in the fourth year Further increments of £180 per annum to be given for any further years in the grade while awaiting consultant posts	£1500 in the first year £1600 in the second year £1700 in the third year £1800 in the fourth year £1900 in the fifth year £1900 in the sixth year £2000 in the seventh year £2000 in the eighth year £2100 in the ninth and any subsequent years
Registrars	£850 in the first year £965 in the second and any subsequent years	£972 8*s* in the first year £1103 19*s* in the second and any subsequent years	£1260 in the first year £1440 in the second year Further annual increments of £180 for each additional year in the grade	£1250 in the first year £1400 in the second and any subsequent years
Junior hospital medical officers	£775 × £50 (6)–£1075	£886 12*s* × £57 4*s* (6)–£1229 16*s*	£1100 × £100 (5)–£1600	£1100 × £60 (8)–£1580
Senior house-officers	£745	£852 6*s*	£1050	£1050 on appointment at age 27 or under £1100 on appointment at age 28 or over
House-officers	£425 per annum for first pre-registration post held £475 per annum for second and any subsequent pre-registration post held £525 per annum for any post held when fully registered	£486 4*s* per annum for first pre-registration post held £543 8*s* per annum for second and any subsequent pre-registration post held £600 12*s* per annum for any post held when fully registered.	Preregistered £555 per annum. Fully registered £635 for first post held. £715 for second post held.	£675 per annum for first post held £750 per annum for second post held £825 per annum for third and subsequen posts

*The British Medical Association also proposed Weighting for part-time service should be re-established at pre-1954 levels Consultants appointed after age 32 should be placed on the scale according to age and experience Domiciliary consultation fees should be increased by 60% The obligation on the whole-time consultant to perform eight consultations per quarter without fee should be abolished.

earnings for the 'significant minority' to which the Spens Committee referred We therefore unreservedly support the continuation of the system "

It adds that at some time in the future selection for C awards might be made regionally

The commission finds nothing surprising in the different proportions of consultants in different specialties who hold distinction awards " Some specialties require more extensive training and experience and involve more difficult techniques and a heavier responsibility than others " On the other hand the commission is not satisfied that the number of awards should always be decided on the basis of percentages of all consultants, and it recommends that for the years 1960–62 awards (on a whole-time basis) be made as follows 100 A-plus awards of £4000, 300 A awards of £3000, 800 B awards of £1750, and 1600 C awards of £750

Senior Hospital Medical Officers

These, says the report have reached the maximum too soon, and this maximum has been too low in relation to other grades The commission recommends as from Jan 1, 1960, the following scale £2000 at age 34 or on appointment later ×£75 (4)–£2300, thereafter increments of £100 every second year–£2700

House-officers

" We consider," says the commission, " that house officers have been greatly underpaid both in relation to their seniors and in relation to what is paid to comparable people in other professions " It recommends a salary of £675 per annum in the first post, of £750 in the second post, and £825 in the third and subsequent posts

Senior Administrative Medical Officers

The maximum of the scale of remuneration paid to senior administrative medical officers in the largest regions should, as until recently, be the same as that of a full-time consultant, with a C award, and the whole scale should consequently be recast

GENERAL PRACTICE

The Pool

In the commission's view, the pool system of remuneration, though unusual, has a number of practical advantages, and recommends a continuance of the system, but not in precisely its present form

" It has been suggested to us by Government witnesses that the pool should be calculated by reference to the number of users of the service rather than of the doctors providing it The main objection to such a change is that it would not be possible, as it is under the present system, to decide upon a level of earnings for the average doctor and be sure of achieving it If the pool were based on the number of patients and not on the number of doctors there would be a tendency, in current conditions, for remuneration to fall, since the population is not increasing as fast as the number of doctors In order to restore the intended level of earnings it would then be necessary to make successive increases in the rate of capitation and other fees No worthwhile public economies would be likely, but doctors' incomes would fluctuate more, which is not a desirable feature in a system of remuneration We therefore recommend that no change be made in this matter, and that the pool continue to be calculated by reference to the number of doctors "

" On the other hand we consider that the balance of advantage lies in the removal from the annual pool calculations of private earnings (from private patients, examinations for insurance companies, part-time industrial practice, and other private sources) Private earnings are very difficult to ascertain on an exact or agreed basis, and it is for this reason that we recommend that the present unsubstantiated figure of £2 million be dropped from the annual pool calculations, and that no attempt be made in future to calculate and allow for annual fluctuations unless there is reason to believe that the alteration has been substantial "

Exchequer contribution to superannuation should no longer be deducted in arriving at the sum payable to doctors The reasons for its inclusion hitherto in the pool have now lost their force

Special inducement payments made to practitioners in certain sparsely populated areas should be taken into account as income from the National Health Service in making up and distributing the pool

The pool should be based on a predetermined average net income from all official sources (excluding the differential payments referred to below), this should be multiplied by the number of unrestricted doctors under 70 in the service, there should be added an annually estimated total figure of practice expenses and subtracted an annually ascertained figure of earnings from hospitals, local authorities and official sources outside the National Health Service

Recommended Levels and Distribution

As from Jan 1, 1960 there should be paid into the pool the sum of £2425 per annum in respect of every practitioner below the age of 70 providing unrestricted general medical services No change is recommended in the general system of allowing for practice expenses

No detailed scheme is suggested for the distribution of the pool, but the report adds the following comments

" First, while we entirely approve of the efforts that have been made, and successfully made, to encourage the formation of partnerships, we feel that the financial incentive at present provided is somewhat excessive Secondly, while we fully approve the policy of giving to the rural practitioner some financial recompense for the facts that he cannot, in a scattered practice, attend so many patients as he could if they lived closer together, and that his expenses in attending them will be proportionately greater, our figures reveal that here again, in England and Wales at any rate, a sound measure has been overdone We accordingly hope that in the scheme of distribution to be worked out the special benefits at present given at the expense of other practitioners to partners and to rural and semi-urban practitioners, while not abandoned, may be relatively somewhat reduced Thirdly, in order to mitigate to some extent the preponderant influence of list size as a determinant of earnings, we hope that, where practicable, greater weight will be given in the scheme of distribution to items other than capitation Fourthly, we trust that the system of initial practice allowances, subject to any appropriate adjustments in amount, will continue to be operated for the elimination of under-doctored areas

" Finally, we regard it as important that the distribution of the pool balance should be made more promptly, and that the amount left to be distributed in this way should be greatly diminished "

It had been suggested that the financial recommendations should be linked to a proposal to reduce the maximum permitted list of patients, but the commission are convinced that this is not a question they are competent to settle, and indeed, such is the variation in human capacity and local circumstance, that they doubt whether anyone is competent to set a fixed and universal limit to the number of patients a doctor should have The absolute maximum must clearly be above the number that it is thought an average practitioner can handle in average circumstances If the maximum should be reduced the revised scheme of distribution that will then have to be made should be so devised as to reduce as little as possible the already inadequate spread of incomes, and as not to cause a substantial reduction in the earnings of individual practitioners already established. In any revision of the regulations regarding list size, care should also be taken not to render it impossible for a practitioner who employs an assistant to find the money to pay him adequately.

General-practitioner Differential Payments Scheme

Over and above the finance needed to meet other recommendations, a special fund of £500,000 per annum should be provided expressly to recognise distinguished general practice by additional remuneration. While leaving the details of such a scheme to be worked out by the profession and the Government, the commission suggest the following:

(*a*) The additional remuneration of a selected general practitioner should be not less than £500 per annum and might well amount to £1000 or even more.

(*b*) Those selected for the additional remuneration should normally continue to enjoy it until retirement.

(*c*) The addition should be treated in all respects as part of the practitioner's National Health Service remuneration.

Assistants

Trainee assistants are paid (indirectly) by the State and it is recommended that for the sum of £775 that was prescribed in 1955–56 there should be substituted as from Jan 1, 1960, the sum of £1150 with such adjustment of the car allowance as may be deemed fair. For other assistants the position is not so simple, since their payment and conditions of service are governed by individual contracts with their principals, and the report does not recommend a standard or indeed a minimum rate. "We trust, however, that the remuneration of assistants will in fact rise in keeping with that of all other young doctors."

Dissenting Report

Prof JOHN JEWKES, in a memorandum of dissent, says:

"... in my opinion, the recommendations of my colleagues in regard to the level of earnings of general practitioners and of part-time consultants will not suffice to restore confidence in these two vital sections of the profession, nor will they provide in the long run an adequate supply of doctors of quality to meet the needs of the service and any improvements that may be sought in it."

Professor Jewkes' recommendations include the following:

1 That the annual earnings of general medical practitioners in the N H S should be based, as from Jan. 1, 1960, on an average net figure (excluding private earnings and the Exchequer superannuation contributions) of £2550, and not on a figure of £2425 as recommended in the report.

2 That no change should be made in the weighting applied to the earnings of part-time consultants or senior hospital medical officers.

3 That no change should be made in the system of distinction awards except that the value of each class of award should be increased by 30%.

4 That fees paid to consultants for domiciliary visits should be increased by 30%, and whole-time consultants should be paid for all such visits.

5 That no retrospective payments should be made to general medical practitioners or to hospital staff.

6 That the new machinery for reviewing remuneration should take the form of an advisory council with somewhat wider functions than those suggested in the report. The council should review remuneration every three years, or sooner if the price level has changed either way by more than 10% from the time of the last settlement.

In England Now

A Running Commentary by Peripatetic Correspondents

WE lament the passing of Charlie. Our part of Lambeth, with its decaying early Georgian dignity, boasts a shopping centre of course, but one which adheres pretty strictly to the Shop Hours Act of 19-whatever-it-was, and if one gets a bit delayed in the Tube not a loaf of bread nor book of verse can one buy. Flasks of wine, obviously, can be purchased at a number of off-licences until 8.30 P.M. and after. Which is why we lament the passing of Charlie. His little shop up our road had a timeless quality. Generations of feet had worn its single step, and though it was scarcely larger than a phone-box Charlie packed into it an infinite number of useful objects from socks via stewing steak to gob-stoppers. He invariably had some kind of remedy for a depleted larder, and his light shone forth until after 9 P.M. "Knock me up if the door's locked," he offered cheerily. "Can't have folk going hungry." At times of particular difficulty, such as a late return on Bank Holiday Monday when the diminutive shelves had long been stripped of comestibles, he has been known to slip back into his cosy little room at the rear and emerge with a lump cut off the end of his own loaf. "Here," he whispered, "have half of mine—tide you over till morning," and then refuse payment. His industry and keen business sense paid off, and as the boutique could not take more than two customers (and then only at some inconvenience and hazard to the precarious boxes of bullseyes) an unruly conclave was to be witnessed in the road from half-past a fine five o'clock as scruffy kids bearing a few pence jostled with returning artisans and hurried housewives to gain entrance to the sanctum.

Yes, we lament the passing of Charlie. Time, woodworm, and rot had taken their toll of Charlie's aged terrace, and the demands of a nearby school for more playgrounds persuaded our Council some 13 years ago to condemn the lot. Lightheartedly we thought we were secure in the Law's delays, but shortly before Christmas the bulldozers moved in. Still shone the light forth, however, and though Charlie no longer troubled to stock up, business was as usual as the dust blew around him and we expected him to go down with his little shop, standing as it were upon the bridge. It was not to be. Charlie went, but with a whimper, not a bang. We glanced over to the usual place, and suddenly saw only the faded cigarette advertisements and a padlocked door. Charlie had folded his tents and crept silently away—and very nicely judged, too, we gather, because the Council had set him up in a much larger establishment three miles away just in time for the Christmas rush. Well, may he prosper, but we shall not see him again. To us his ghost lingers over the spot where asphalt will be laid and where children will soon play marbles and suck bullseyes.

* * *

A professor we know is not very good at answering letters, so a month or two ago we sent him a Mallaig kipper in a plain envelope. Yesterday we made a quick inspection of the correspondence compost heap on his enormous desk. The kipper has not yet surfaced, though our olfactory organs noted that its presence is becoming perceptible. But this is clearly the wrong approach. We should have remembered Sherrington's teaching that the sense of smell—"rich in affective tone"—quickly adapts and loses interest after the first encounter.

Now we have hit on a better plan. A firm of paper-makers has obligingly prepared for us, by a secret process, some special notepaper guaranteed to ignite spontaneously after 4–6 weeks. We are awaiting the result of this experiment with interest and hope that *The Lancet*, having accepted this preliminary communication, will be prepared to publish our full report in due course.

We expect, at least, to earn the gratitude of the professor by clearing his desk of unopened advertisements for Totamicin.

* * *

Last month I sat the examination for the membership of the Institute of Advanced Practitioners (M I A P) It is conducted by retired Civil Servants from the Ministry of Health The practical tests vary according to the type of practice The urban practitioner, for instance, may be given a number of passport photos to compare with standard subjects in a given time and make the appropriate comment on the backs, the rural doctor on the other hand may be given a bundle of E C 10s to sort into packets of a hundred or a given number of old ointment jars to wash out in a specified time Two of the questions from my written paper were

(1) Write brief reasons for any two of the following—Med 2a, OSCI, FW 8, BM 4(Rev), DMO

(2) The Ministry decides that seamless fine-thread two-way-stretch thigh-length hose shall no longer be prescribable Discuss an alternative treatment for chilblains

In my viva I was asked to give the percentage of the shillings collected on prescriptions which I allocated to my wife's pension fund, to dictate a letter to the National Assistance Board for a grant towards extra coal for a patient's television viewing-room, and to name the last five Ministers of Health in the correct order

I passed, paid my first annual subscription of 18*s*, and can now display a neat red-tape bow on the chest-piece of my stethoscope and the Institute's badge on my car This depicts a graduate in tattered academic dress discreetly manacled to an executive council clerk whose neat suit is unmistakably Savile Row

* * *

As a peripatetic psychiatrist I recently visited an Ayurvedic mental health research department, supervised by a scholarly Brahmin who is a pandit of the Vedic texts His assistant demonstrated the patients under their care, and his sweeping therapeutic optimism disarmed my dubiety about the potions, and the glutinous pastes for external application to the head, which were his principal medicaments At least the principle of *primum non nocere* seemed to be observed, and in psychiatry that is something

The pandit himself obliged with a brief outline of Vedic teachings on abnormal psychology On being asked whether he had difficulty in communicating with his Western-trained colleagues, he explained that he was even now studying Dr Curran's introductory textbook With a beatific smile, he pointed to the heavens and said " God bless him for his simple lucid explanations!" I have never heard any textbook receive such a heartfelt recommendation

* * *

DEPRECIATION

Look—there's plenty to do when you're thirty
Though the shadows are gathering fast
You may think that we old 'uns have had it,
You may think that we live in the past,
But old age makes a fellow more willing
And he'll work, just as long as he'll last

Now the way to survive when you're thirty
Is to plan for it, right from the first
You must Live while you're young—but not *too* much—
To get rid of Youth's feverish thirst,
And then stock up your mind for retirement,
It's the thoughtless ones feel it the worst

You don't squander yourself, when you're thirty—
You must always make sure of your sleep
Lord! The way you see some of 'em living
It's enough for the angels to weep,
But with care you can keep up your walking—
In the parks, where the hills aren't too steep

It's important to plan, when you're thirty,
You must *spread* yourself over your week
And you mustn't pay too much attention
If you notice your vertebræ creak,
And if ever you're hustled by youngsters—
Just you turn a deaf ear to their cheek[1]

Letters to the Editor

MEDICAL NEEDS OF INDIA

SIR,—I was glad to read your editorial of Jan 30 in which you draw attention to the vast problem of India's medical needs

As one whose professional career for 31 years has been spent almost entirely in North India, I should like to endorse much of what you say, and also to emphasise the need of help from outside India In this connection I think two statements in your article may give a wrong impression, and thus tend to discourage any who might feel disposed to offer to serve in India

" Though some of the missionary hospitals and schools were outstandingly good and these continue—for example, Vellore, which has plenty of candidates for its medical school—the Government does not look with favour on missionary effort" It is true that the Government of India does not encourage the initiation of entirely new ventures, but I know of no restrictions placed on existing medical missionary work, and no interference with the running of medical institutions While there may be the occasional unfriendly official, the policy of the Central Government seems rather to encourage mission hospitals, many of which receive financial assistance, recurring or otherwise

The following figures taken from the latest edition of *The Christian Handbook of India*, give some idea of the present strength of mission hospitals run by Protestant bodies

Total no of hospitals	238
This includes	
Those of over 50 beds	60
" " " 100 "	55
" " " 150 "	14
" " " 200 "	7
" " 350 ,	4

There are many smaller units, and all have comparatively large outpatient departments

In addition there are 11 tuberculosis sanatoria and 52 leprosy institutions

Many of the larger hospitals are training nurses and are recognised by the Government for this purpose The nurses take the examinations of the local provincial Government

There are numerous dispensaries and some hospitals at work in village districts—that " backward countryside " where, as you rightly point out, the need is greatest

I was once personally assured by a Government official of some importance that the type of work being done by these small medical mission units is what is needed, and is commendable in his opinion

Your second statement, that " even medical missionaries are being slowly eliminated as replacements fall due, fewer being allowed to enter than to leave," does not accord with the facts

In its policy relative to the entry of foreigners into India the Government has shown no discrimination against medical missionaries, and no difficulties are placed in the way of those returning to their mission posts from leave in Great Britain.

The admission of non-Commonwealth persons is subject to certain restrictions, however, but these apply equally to all, whether medical or non-medical, missionary or otherwise

It is true that the total number of medical missionaries is smaller than some years back, but this is largely due to a lack of new volunteers Another cause is the deliberate policy of mission hospitals in appointing Indians to posts of responsibility wherever possible, but this is an entirely voluntary matter

The door of opportunity for medical service in India is still open, especially to those with a missionary vocation

E JOYCE ROBINSON
Bible Churchmen's Missionary Society,
Kachwa
District Mirzapur,
Uttar Pradesh,
India

Lowestoft

SAFETY-HARNESSES IN CARS

SIR,—We have read with interest Mr Barrett's article of Feb 6 on the early treatment of stove-in chest. We notice that he does not mention the importance of safety-harness in cars, which in our opinion would have been a major factor in the prevention of these injuries Mr Barrett states that "death steps in unnecessarily" We agree most of these deaths could have been prevented.

The commonest cause of these accidents is the driver or passenger being thrown forwards on to the steering-wheel or dashboard. This forward movement, which often includes the seat, could be prevented by a well-designed pelvic or pelvic-shoulder harness which is bolted to the floor with a reinforced steel plate some distance behind the front seat. This harness must be fitted with nylon webbing capable of withstanding a strain of several thousand pounds

In addition, we should like to point out that in a detailed analysis of road accidents, over 30% of passengers are thrown out of the car at the moment of impact because the doors of the car spring open. These injuries, too, would be prevented by adequate pelvic or pelvic-shoulder harness

It is, however, important that such harnesses be constructed of strong material; well designed, and securely bolted to the floor Cheap materials, shoddy buckles, and belts which are looped around the back of the seat are utterly useless

London, W 8

G P ARDEN
D M WALLACE.

THE THORN IN THE FLESH

SIR,—Following Dr Buhr's article (Feb 6), this case-report shows that a generalised allergic response may follow injury by the thorn of the blackthorn.

A housewife, aged 61, was admitted to Southmead Hospital on Sept. 24, 1959, with the history that, while blackberrying three days previously, she had scratched her arm on a blackthorn bush (she was emphatic that it was blackthorn rather than blackberry) A few hours later she developed an irritating rash at the site of the scratch, which spread within a few hours to involve the whole arm, and then the rest of her body, at the same time she became increasingly short of breath She was previously in good health, and there was no personal or family history of allergic disease or asthma

On admission she was dyspnœic at rest, with a respiratory-rate of 46, and slightly cyanosed Her temperature was 100°F Her whole body was covered in a vesicular rash, secondarily infected in places Examination of her chest showed pronounced expiratory effort, supraclavicular recession, generalised bronchospasm, and occasional, scattered rales

Investigations showed a white-cell count of 14,400 per c.mm. (8% eosinophils, absolute eosinophil count 1150) Chest X-ray was normal

Her bronchospasm and urticaria settled only slowly with 'Franol' (ephedrine, phenobarbitone, and theophylline) and chlorpheniramine, and she was fit for convalescence only after 18 days' inpatient treatment.

I am grateful to Dr Francis Page for permission to publish details of this case, which was under his care

Southmead Hospital
Westbury-on-Trym, Bristol

B A LATHAM

SIR,—Dr Buhr's article was most interesting for blackthorn injuries are by no means uncommon in agricultural districts and prompt me to record this case

A schoolboy, aged 9, was seen in the casualty department of High Wycombe Hospital on June 20 last year He had fallen, injuring his left elbow, and had tenderness at the lower end of the humerus, with a full range of movement. There was no skin wound and X-ray revealed no bony injury He was treated with a collar-and-cuff sling, and by June 30 was completely symptom-free.

On Oct. 16 he returned complaining of a lump in the left arm. There was a small mobile mass over the postero-medial aspect of the left humerus which was apparently in the triceps muscle. This mass was tender and thought to be an encysted hæmatoma resulting from the injury in June No immediate treatment was advised. By Nov 13 the tumour was slightly larger and still tender and mobile Excision was advised, and on Nov 24, 1959, with a bloodless field, the lump was explored and proved to be a mass of fibrosis (approximately $\frac{3}{4} \times \frac{3}{4} \times 1\frac{1}{2}$ in.) in the triceps muscle. The specimen was cut open at the end of the operation and a $\frac{1}{2}$-in. tip of a blackthorn was revealed. The wound healed satisfactorily, and when last seen the patient had no disability

Section of the specimen showed "fat necrosis and granulation tissue containing some brown pigment suggestive of old hæmorrhage and a number of areas of foreign-body reaction"

This case is interesting in that there was no skin wound and nothing to show the entry of a foreign body It illustrates a profuse foreign-body reaction which was stimulated by blackthorn.

I am grateful to Mr G J Walley for permission to record and treat this case.

The General Hospital,
Burton-on-Trent.

P C CASHMORE.

TREATMENT OF INGUINAL HERNIAE

SIR,—I think Mr Moloney (Feb 6) is undoubtedly right in stressing the extra care that is taken with recurrent herniæ In considering this problem of herniorrhaphy it is pertinent to recall that most recurrences after indirect herniæ are indirect herniæ again, and although we may be certain we have removed the sac high enough at the first operation, when the recurrence appears well within the first twelve months we might well ask ourselves where has this new sac come from?

Consideration of this over the last three years has led me to look for, and often find, lax peritoneum on the medial side of the neck of the sac which can be drawn out by hooking the medial half of the neck over the first joint of the index finger In this way the peritoneum can be rendered as tense on the medial side as it is naturally on the lateral side. In this way I find I am removing more sac than I had done previously

The second problem in the initial repair of herniæ is the securing of absence of tension on the repair particularly in the lateral part of the posterior wall, and if the absence of tension is being secured by release of the ligament from the fascia lata, from below rather than from above (Tanner slide), then simple pressure upwards with the finger after the repair is completed at the site of the internal abdominal ring will determine whether or not the ligament is being pulled down by any residual attachment of the fascia lata to it laterally

If the impression is that there is still tension from below then it is necessary to further release the fascia lata laterally from its attachment to the fibres of the external oblique at its lower border. Confirmation of absence of tension using this method of repair can be gained if the patient is made to cough during the anæsthetic at the end of the operation when free movement of the lower border of the external oblique upwards will be seen to occur if there is no pull from below

This principle of absence of tension applies equally to any form of repair or reconstruction, including a nylon "darn" It particularly applies if the mobilised ligament is being sutured up to the conjoint tendon after release from the fascia lata.

The Memorial Hospital
Peterborough

D W BRACEY

HIGH PLASMA-IRON IN PORPHYRIA

SIR,—Dr Hathorn and Dr Lamont (Jan 30) refer to high values of plasma-iron found in cases of porphyria (? acute intermittent porphyria) in Africans, and ask if plasma-iron has been measured "in cases with other types of porphyria"

In my translation of Vannotti's book,[1] it is stated that in acute intermittent porphyria a fairly regular increase in serum-iron has been found,[2] values ranging from 120 to 220 µg per 100 ml, and also iron deposition in the organs In his recent survey, Goldberg [3] found that the hæmoglobin in 27 cases of this disease lay within normal limits

The extensive deposition of iron in the organs of the congenital porphyria patient, Petry, is well known from the classic investigation of Borst and Königsdörffer [4] Two forms of iron-containing deposit were observed, hæmosiderin and a form in which iron was associated with a brown, amorphous pigment Quantitative serum-iron analyses are not available

In a case of cutaneous porphyria with easily traumatised skin and formation of bullæ, Langhof and Mildschlag [5] reported very high serum-iron values

Whilst it is difficult to interpret these findings with certainty, it is clear that iron metabolism may show signs of abnormality in the various porphyria diseases The role of iron in normal porphyrin [6] and hæm [7] formation is being very actively investigated at the present time in several different laboratories

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C RIMINGTON.

URINARY EXCRETION OF PORPHOBILINOGEN IN ACUTE PORPHYRIA

SIR,—It is well known that acute intermittent porphyria is more common in females than in males It is also known that in patients with acute porphyria attacks are provoked by endocrine imbalance Durst and Krembs [8] and Hughes [9] described instances of attacks during pregnancy and the puerperium Levit et al [10] recorded a case of acute porphyria with premenstrual attacks and exacerbations caused by progesterone injections More than a year ago we also observed two attacks in connection with endocrine dysfunction in a 46-year-old woman suffering from acute porphyria This presumably climacteric patient had had two periods of amenorrhœa, each lasting about six months and ending in menstrual bleedings and attacks of porphyria [11] With the determination of the daily output of the porphyrin precursor, porphobilinogen (P B G), in the urine, it was possible to demonstrate in this patient some relation between porphyrin metabolism and endocrine imbalance

We followed this patient for three months, beginning about nine months after her second attack, and we determined the daily P B G output in the urine by the method of Mauzerall et al [12] slightly modified The accompanying figure shows the daily P B G levels in the urine

In the first weeks of observation the patient had no menstrual bleedings (her last bleeding was in March, 1959) and no high urinary P B G levels either However, 14 to 16 days before her first (July 3–5, 1959) and second (Aug 2–5) bleeding there was an increase in the urinary P B G level Thus the period of high urinary P B G output coincided with ovulation During high urinary P B G excretion her clinical state deteriorated slightly, especially before her first bleeding

During our observation period a third bleeding has not been reported and she is again amenorrhœic Urinary P B G levels are not high

Our observations show that in this patient 14 to 16 days before bleeding after a period of amenorrhœa the P B G excretion in the urine increased This increase coincided with the time of ovulation The increased urinary P B G levels before the patient's first bleeding were similar to those observed during her attacks (140–165 mg per day) We suppose, therefore, that in this case endocrine imbalance plays an important role in precipitating attacks of porphyria

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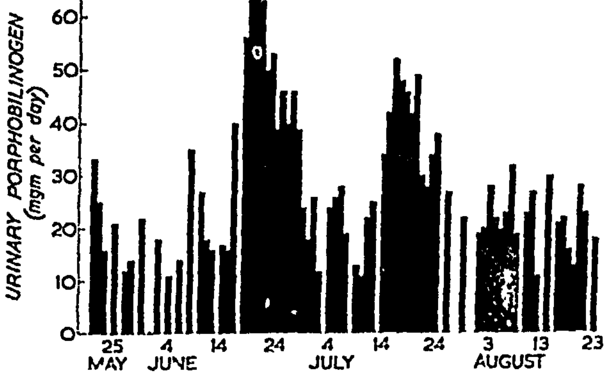

Daily porphobilinogen levels in urine

AUTOIMMUNE HÆMOLYTIC ANÆMIA WITH RENAL FAILURE DUE TO PHENACETIN AND P A S.

SIR,—Your issue of Jan 2 contained an article on this subject by Dr MacGibbon and her colleagues Because of the rarity of such cases I should like to report another case [13] of a hæmolytic reaction due to *p* aminosalicylic acid (P A S)

A 57-year-old man suffered from pulmonary tuberculosis for several years He had been treated with different antibiotics and with P A S Oral P A S was badly tolerated (vomiting, general malaise, and fever) It was therefore decided to give a P A S solution intravenously (15 g daily) with 250 mg of oxytetracycline His clinical condition improved, but at the beginning of the 10th infusion of P A S he had a violent reaction (lumbar pain, rigors, vomiting, and collapse), and the infusion was immediately stopped He became very anæmic, the hæmoglobin fell to 48%, the serum-bilirubin increased, and the red cells showed anisocytosis and spherocytosis After three days, when the patient was already recovering, we received the blood for serological investigations

Blood group B, Rh negative, direct Coombs test negative

Besides incomplete Rh antibodies anti D, apparently the result of transfusions with Rh positive blood, the serum contained a second antibody This antibody agglutinated the cells of the patient and other Rh negative subjects, but only in the presence of P A S

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4 Borst M, Königsdörffer, H Untersuchungen über Porphyrie, p 257 Leipzig, 1929
5 Langhof H, Mildschlag, G *Arch Derm Syph* 1954, 199, 21
6 Brown E G *Nature, Lond* 1958, 182, 313
7 Heikel T Lockwood W H, Rimington, C *ibid* p 313, Goldberg, A *Brit J Hæmatol* 1959, 5, 150, Faber, M, Falbe Hansen, I *Nature, Lond* 1959, 184, 1043
8 Durst, J B, Krembs, A *J Amer med Ass* 1956, 160, 165
9 Hughes R T *Lancet*, 1957, i 301
10 Levit, L J, Nodine, J H, Perloff, W H *Amer J Med* 1957, 22, 831
11 Kelényi G Arató G, Buda V *Orv Hetil* 1959, 100, [illegible]
12 Mauzerall D Granick S *J biol Chem* 1956, 219 435
13 van Loghem J J Jr [illegible] International Congress of Clinical Pathology Brussels, July, 1957

No agglutination could be obtained when the other drugs which the patient had received (oxytetracycline, isoniazid, penicillin) were added to the patient's serum. In the maximal concentration of P.A.S. (500 mg. per 100 ml.) optimal reactions were obtained (titre 32). As the concentration of P.A.S. diminished the titre fell gradually. The antibody was still active after heating at 56°C for 20 minutes, but was destroyed by heating at 70°C for 10 minutes.

Hæmolysis could not be demonstrated with fresh serum samples, nor with inactivated serum samples to which human or guinea-pig serum had been added as a source of complement. The antibody in the patient's serum was not neutralised by the addition of P.A.S. solution to the serum, nor could it be removed by adsorption on to packed cells, but it was completely removed after the addition of P.A.S. + red cells.

It seems well established that the antibody developed in the course of the treatment by intravenous injection of P.A.S., because repeated oral administration of P.A.S. was never followed by signs of abnormal cell destruction, and also because the antibody disappeared a few weeks after the intravenous P.A.S. was stopped.

Another case of autoimmune hæmolytic anæmia induced by P.A.S., this time by oral treatment, was recently observed by Dr. J. Dausset in Paris (unpublished observations).

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Amsterdam.

J. J. VAN LOGHEM, Jr.

SIZE DIFFERENCES AND SOCIAL CLASS

SIR,—In your editorial of Feb. 6 on the Germ-free Animal you say that the difference in size between adolescent boys in social class I and those in social class V is no longer seen. I believe this statement to be in error, as reference to the texts on growth[1] or to the original literature[2] will readily show. On the contrary, the most striking thing about the changes in growth-rate which have occurred in the past fifty years is that *all* social classes are growing up earlier and that the difference between the classes, though it may have decreased a little, has not decreased as much as many of us would expect. One is reminded of the parallel situation in infant mortality described recently by Professor Morris and his colleagues in your pages. The reasons for the social class differences in growth-rate and in final adult size are evidently not simple, and the subject invites much more careful research.

Institute of Child Health,
London, W.C.1.

J. M. TANNER.

PRESERVATION OF MEDICAL RECORDS

SIR,—Your article (Feb. 13, p. 379) drawing attention to the British Records Association memorandum on the disposal of medical records is welcome. The historian and archivist have a legitimate interest in medical records which should be as far as possible respected.

Medical records are more than archives, however, and for half a century or so may help to preserve the lives and limbs of those to whom they refer, if they are intelligible and accessible. The growth of procedures in modern medicine is reflected in increasingly complex medical records. In this hospital the mean number of sheets recording a single admission was 9.3 in 1946, 12.6 in 1952, and 18.9 in 1956, although the mean duration of admission fell slightly during that time. If the information thus recorded is to play its full part in exhibiting all features of an illness to those caring for the patient, either then or later, the record must be more than a sheaf of papers arranged at hazard.

The increasing bulk of medical records makes microfilming a likely solution to the problem of storage; microfilming is most effectively applied to a record system designed for it, precautions being taken to preserve documents in a physical state that permits microfilming without laborious preliminary treatment.

With these two requirements of medical records in mind we have designed a system of clinical records which has been in operation at the United Cardiff Hospitals since April, 1958; it is proposed that microfilming of the new records will begin when they are 5 years old.

Cardiff Royal Infirmary.

A. H. JAMES
JOHN MORGAN.

POSTOPERATIVE DIARRHŒA

SIR,—A further point must be made concerning postoperative diarrhœa and Mr. Schofield's letter of Jan. 16. It is only in subacute intestinal obstruction, which may or may not occur postoperatively, that an intestinal hurry has been demonstrated using methylene-blue. Two charcoal biscuits taken orally have also been employed to demonstrate this faster intestinal transit time. The latter material does not diffuse and the same results occur.

London, W.1.

J. J. SHIPMAN.

TOLBUTAMIDE IN THE TREATMENT OF ANGINA PECTORIS

SIR,—We were most interested to read the report of Professor Singh and Professor Bardhan (Dec. 19) on progressive improvement in angina pectoris in 9 diabetics and 15 non-diabetics treated with tolbutamide. Of interest to us, also, was their observation that the beneficial effect of the drug was not directly related to its hypoglycæmic effect.

Early in our work with sulphonylureas we noticed that patients given tolbutamide experienced a feeling of general stability and wellbeing which was not related to the hypoglycæmic action of this compound, since it was observed even in those patients whose hyperglycæmia and glycosuria were not improved by such therapy. It was also observed that shortly after institution of tolbutamide therapy some patients suffering from angina pectoris experienced an unanticipated relief from their painful attacks and were able to reduce or to eliminate entirely the use of nitroglycerin. These studies were reported[1] in May, 1958. Subsequently, we noted that patients afflicted with intermittent claudication were also benefited by the use of tolbutamide, as shown by marked increase in claudication time or even complete disappearance of the pain on walking.

In a paper which is now in press (*New York State Journal of Medicine*) we reported on a group of 41 patients with angina and/or claudication treated with tolbutamide for periods of twelve to forty-two months. Among them were 18 suffering from angina pectoris, 20 with intermittent claudication, and 3 with both conditions. 5 patients were given tolbutamide in conjunction with insulin, and the other 36 tolbutamide without insulin. Relief from pain was obtained in 16 patients with angina, in 15 with claudication, and in the 3 patients suffering from both conditions. However, we should like to emphasise that in all our patients who were relieved from pain of angina and/or claudication, the drug had no effect on the associated cardiovascular disorders. Specifically, it did not lower the blood-pressure in 10 patients with hypertension, and failed to prevent myocardial infarction in 2 and diabetic gangrene which necessitated an above-the-knee amputation in 1 patient.

Following the successful use of tolbutamide in diabetics with angina and intermittent claudication, we employed this drug in such conditions in 8 subjects with latent diabetes—that is, subjects with abnormally high glucose-tolerance curves but free from glycosuria and from clinical manifestations of diabetes, and in 10 non-diabetic persons. Beneficial results were noted in both groups, but our series of such patients is not large enough for a definitive evaluation of the observed benefits

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[1] Growth at Adolescence. Oxford, 1955.

[2] Social Implications of the 1947 Scottish Mental Survey. London, 1953. Berry, W. T. C., Cowin, P. J. Brit. med. J. 1954, i, 847; Hammond, W. H. Brit. J. prev. soc. Med. 1957, 11, 131.

[1] Metabolism, 1958, 7, 243.

The mechanism by which the sulphonylureas may produce relief from pain of angina and claudication has not been established yet Singh and Bardhan state that the benefit in their patients with angina may be accounted for by the reduction of blood-lactic-acid by the drug One possibility that we have considered in our patients relates to the influence that the drug may have on the metabolism of serotonin and that of adrenaline and noradrenaline Studies designed to clarify these points are now in progress in patients with angina and/or claudication, and will be reported in a separate communication

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MAXIMILIAN FABRYKANT
BENJAMIN I ASHE

CHRISTMAS FACTOR IN THROMBOTEST

SIR,—Dr Nour-Eldin (Dec 12) repeats his claim that the thrombotest is not sensitive to Christmas factor I can only reply by giving the evidence on which I base my contention that it *is* sensitive

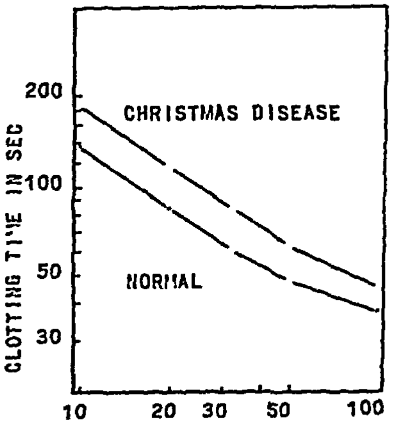
(1) Fig 4 in my paper (Nov 7) shows a dilution curve for plasma from a patient with Christmas disease This experiment was designed to imitate the effect of a disproportionate reduction of the Christmas factor during anticoagulant therapy The experiment shows that the thrombotest is sensitive to Christmas factor under these conditions

(2) The following figures give the results of thrombotest estimations in 10 patients with verified Christmas disease, all with characteristic joint bleedings

Case	*Christmas factor*	*Thrombotest*	*Case*	*Christmas factor*	*Thrombotest*
1	1·5%	63%	6	<1·0%	38%
2	1·0%	72%	7	<1·0%	48%
3	1·0%	44%	8	<1·0%	60%
4	<1·0%	72%	9	<1·0%	48%
5	<1·0%	65%	10	<1·0%	62%

Patients 1–5 were studied at the Institute for Thrombosis Research, the University Hospital of Oslo, and patients 6–10 by Dr Inga Marie Nilsson, the University Hospital (Almänna Sjukhuset) of Malmö, Sweden These studies show that the thrombotest gives abnormally low results in these patients However, I agree that the test is not sensitive to Christmas factor when the concentration of this factor is above 10% (see fig 4 in the original paper) Patients with mild Christmas disease may therefore have thrombotest values in the normal range

(3) In the accompanying figure the lower curve is the usual correlation curve of the thrombotest, obtained by diluting normal standard reference plasma The upper curve shows the result obtained when plasma from a patient with severe Christmas disease (Christmas factor less than 1%) is diluted in the same manner The difference between the two curves indicates the sensitivity to Christmas factor at different levels of the other clotting factors The two curves differ by about 50%,—in other words, if the *Christmas factor is reduced out of proportion to the other factors,* the thrombotest value will be as much as 50% lower than it would otherwise be At a level of 10–20% of the other adsorbable factors, the clotting-times will increase rapidly when the Christmas factor is further reduced



Dilution curves for normal and Christmas-disease plasma The curves are drawn on double log paper

The thrombotest method is designed for the control of anticoagulant therapy The main point of interest is therefore the sensitivity to Christmas factor at a low level of the other adsorbable clotting factors The presented evidence indicates that the test rapidly detects a disproportionate reduction of the Christmas factor during anticoagulant therapy, since the thrombotest times will then increase For example, if a patient has a reduction of all four factors to 15%, and the Christmas factor then is further reduced, the thrombotest value will drop below the 10% level This, of course, is exactly the warning the clinician asks for

Thus, the sensitivity to Christmas factor is definite, but not as high as that of a specific test system This follows necessarily from the fact that the test is also sensitive to the extrinsic system Any test which is sensitive to both the extrinsic and intrinsic system must be less sensitive to deficiencies in only one of these systems than specific tests for each system However, this sensitivity is sufficient for controlling anticoagulant treatment The thrombotest method has never been recommended as a method for disclosing Christmas disease, nor for the quantitative determination of Christmas factor For this purpose methods must be used which reflect changes only of the intrinsic clotting system and not a combined test for the intrinsic and extrinsic systems such as the thrombotest

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Oslo

P A OWREN

HIGH-PROTEIN DIETS

SIR,—In his letter of Dec 19 Dr Garrow says that I imply in my paper[1] that a retention of 50 g of nitrogen does not benefit the cachectic patient This retention was induced quickly, in 7 days, in surgical cancer patients and did not increase the albumin pool

As a worker in this field himself this finding should not have prompted such an interpretation from Dr Garrow An equilibrium between fixed tissue protein, as judged from body-weight or nitrogen excretion, and plasma-protein has been shown in dogs during both depletion by plasmapheresis[2] and repletion and maintenance by parenteral plasma injection[3] In each situation, however, a lag period occurred during which "reserve protein" was raided or restored It is certainly not incorrect to say that "lean muscle mass probably varies with the circulating protein mass," and Dr Garrow himself has recently shown a concomitant loss of plasma and tissue nitrogen in starved dogs[4]

The rapidity of turnover and low plasma-albumin observed in two patients with high gastrointestinal malignancy is surely contributed to by gastrointestinal protein leakage, as suggested by Dr Schwartz and Dr Jarnum (Dec 19) I prefer to believe both groups of workers are partially correct albumin is being "flushed" through the circulation to depleted tissues (Garrow) and being leaked into the gastrointestinal tract from the malignancy (Schwartz and Jarnum) This latter I have referred to as an internal protein shunt I should still hope to see direct correlative measurements between positive nitrogen balance and net gain in tissue-protein mass to substantiate the former

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R F MADDEN

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CATHETER DRAINAGE AND INFECTION IN ACUTE RETENTION OF URINE

SIR,—With interest I read the investigations of Mr Ashton Miller and his colleagues (Feb 6) in their endeavour to reduce the incidence of infection in patients admitted with acute retention

The method of sterilising the bottle, which I shall adopt, is excellent and simple, but I feel that the catheter-cum-connector-cum-rubber-tube falls far short of perfection Although the size of the catheter is not stated, those in common use encourage urethritis and ascending infection by virtue of their size and material The glass connector is often insecure or dismantled by meddlesome patients, or is pulled on by the heavy and insecurely anchored three feet of rubber tube

For the past year or more I have been using Gibbon's polyvinyl chloride 'Portex' catheter,[1] which, being five feet long, obviates any glass connections When passed with the usual aseptic and non-touch technique, urine immediately, by bladder pressure and capillary action, passes down the catheter before there is time to withdraw the obturator The non-irritating material lying loosely in the urethra minimises urethritis Air bubbles have little chance of ascending into the bladder, and subsequently the action of the small tube is syphonic.

Although I have not done routine cultures on all patients, it is gratifying to see how many arrive in the theatre with sterile urine, even after ten days

King's Lynn J O HARRISON

DANGER OF THE ABBREVIATION P.A.M

SIR,—In your leading article[2] on organophosphate poisoning, there were a number of references to the use of P.A.M (pyridine-2-aldoxime methiodide) in the treatment of this condition I drew attention[3] in 1958 to the danger which might arise in confusing this substance, under this abbreviation, with the much more widely used preparation of procaine penicillin with 2% aluminium monostearate also known as P A M, and the type of penicillin used for the treatment of yaws in mass-campaigns W H O Information Circular No 2 (January, 1959) on Toxicity of Pesticides to Man (p 8) also draws attention to the danger of confusing the two preparations, and it has been referred to elsewhere

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THOS C LONIE
Acting Executive Officer for Health.

TREATMENT OF TROPICAL EOSINOPHILIA

SIR,—The article by Dr Baker and his colleagues (Aug 22) was of particular interest to me, because our own work on similar lines was published in 1958[4]

151 patients in our series were divided in the following eight groups

(1) No treatment Minimum period of observation 1 month, 30 patients
(2) Diethylcarbamazine 13 mg per kg daily for 4 days, 13 patients
(3) Diethylcarbamazine 13 mg per kg daily for 8 days, 6 patients
(4) Diethylcarbamazine 6 mg per kg daily for 4 days, 16 patients
(5) Diethylcarbamazine 6 mg per kg daily for 8 days, 23 patients
(6) Diethylcarbamazine 3 mg per kg daily for 8 days, 17 patients
(7) *Diethylcarbamazine 26 mg per kg for 1 day only, 19 patients*
(8) Carbarsone 0 26 g twice daily for 10 days, 27 patients

Improvement after treatment was judged on the basis of amelioration of presenting symptoms and the degree of fall in initial total eosinophil-count.

None of the patients in the control group kept without treatment had genuine relief Diethylcarbamazine was uniformly effective in lowering the total eosinophil-count and in producing symptomatic cure in the majority of patients Almost all th dosage schedules gave favourable results but minor variation were seen in the degree of effectiveness We observed that th administration of 6 mg per kg of diethylcarbamazine daily fo 8 days produced the best results It is surprising to note ho close is this dose to that of 5 mg per kg for 7 day recommended by Dr Baker

The results in the diethylcarbamazine groups did not diffe significantly from those in the carbarsone group Relief o symptoms, however, was usually felt earlier with the diethylcarbamazine group

Dr Baker and his colleagues hint at the possibility of treatment with a single large dose of diethylcarbamazine. We trie a single dose of 26 mg per kg and found that this schedul worked equally well

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R D GANATRA

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[1] Gibbon, N *Brit J Urol* 1958 30 1
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POLIOMYELITIS VACCINATION: DOSAGE AND TECHNIQUE

SIR,—I was interested in a suggestion in your leadin article of Jan 9 that the immunological response to th vaccine in the community may not be so effective a theoretical considerations would indicate I should lik to raise a practical point, small perhaps, though no entirely unimportant, in the carrying out of immunisatio programmes

Personal experience with the difficulties encountered i giving a full dose from a 1 ml. vial in poliovaccination has le me to make inquiries into the literature and to have discussion with colleagues, from which it appears that it is of som importance that the full dose be given. I blamed my ineptitud in getting the full dose out of the 1 ml vial, but I found that even with great care, success was sometimes difficult. I wa interested to hear from others, who were expert, that they to had had difficulties

Several authorities (including Salk) are firmly of the opinio that the immunity response is proportional to the mass o antigen injected. It would appear that the important type- component of poliovaccine does not always produce a satisfactory immunological response. As with other antigens individuals vary in the response to a given dose. For these and for other reasons, it is important that the full dose should be given.[1] [2]

Independent investigation by the Salford City Analyst has shown that the amount of poliovaccine in the 1 ml vials was always above 1 1 ml (The lowest average in the series tested was 1 104 ml.) In other words, there appears to be an "overage" in the vial—as is indeed the stated practice of the manufacturers in conformity with the recommendation of the *British Pharmacopœia*—so the manufacturers have played their part.

Particularly when using the 1 ml. vials, care is needed to see that the subject receives an adequate dose Losses, some of them almost inevitable under "field" conditions, and in busy surgeries and clinics, may be due to the following causes

The quantity of vaccine left in the nozzle of the syringe after use is surprising in amount, as can be proved by examination of the contents of the barrel after withdrawing the plunger after injection

There is also a quantity of vaccine left in the needle and holder

In addition there is loss due to inability to get all the vaccine down from the neck and head of the vial Perhaps with many volunteers waiting one should not expect that every doctor will spend a long time, which is sometimes necessary, in flicking the whole of the vaccine down

Some doctors use a special withdrawal needle to draw up the vaccine, here is another possibility of loss

There is hardly sufficient vaccine in the vial to cover losses when many bubbles have to be expressed

There may be loss from leakage after inoculation from the puncture in the skin

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[1] *Brit med J* 1959, i, 609
[2] *ibid* 1958, i, 1206

Experience has shown that under conditions of every-day practice, some volunteers have got less than 1 ml , occasionally far less than 1 ml

When it is remembered that different batches of vaccine are known to vary slightly in potency, it is to be hoped that the potency of the vaccine will be increased in future so that even with a smaller dose adequate immunity may still be obtained Until this is possible, it is wise for special care to be taken in technique in order to reduce avoidable losses in important and costly antigens

Health Department,
Salford

J L Burn
Medical Officer of Health

EFFECT OF MODIFIED EGG-YOLK FATS ON BLOOD-CHOLESTEROL LEVELS

Sir,—In a preliminary communication [1] we reported the modification of egg-yolk fats brought about by feeding sunflower-seed oil to hens A considerable increase (from 5 65% to 30 4%) in the di- and tri-unsaturated fatty acids was noted, and dietary trials of the " unsaturated " eggs in 2 subjects suggested that they might be consumed without raising cholesterol levels above the basal values achieved with a low-fat diet But Gordon et al [2] found no difference between the cholesterogenic effects of " normal " and " unsaturated " eggs, when ten yolks per day were fed

Additional dietary trials have now been carried out using both natural base diets low in fat (4% of calories) and the liquid-formula type of diets Our subjects were healthy medical students and interns who carried on with their normal activities during the test

Natural food base (low-fat) diet —Two subjects received the basal low-fat diet for 2 weeks Ten " unsaturated" yolks were added per day for a further 2 weeks, the diet being held isocaloric by reduction of its carbohydrate content At the end of this period, the basal low-fat diet alone was continued for 10 days, and then ten ordinary yolks were added per day for a further 2 weeks Their response was as follows

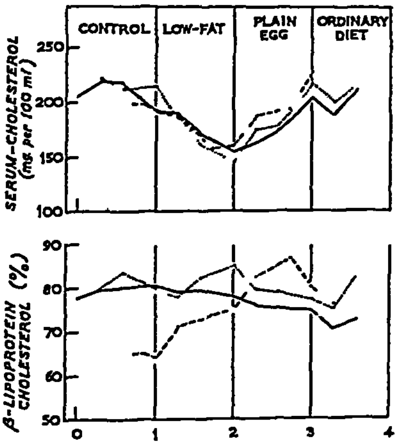

Fig 1—All 3 subjects showed a fall in serum-cholesterol during the low-fat phase Changing to the ordinary-egg formula resulted in a prompt rise of serum-cholesterol back to control levels in 2, and a slight overshoot in the 3rd

Diet	*Duration*	*Serum-cholesterol (mg per 100 ml)* *Subject 1*	*Subject 2*
Control	1 wk	241	156
Low-fat basal	2 wk	180	124
Basal plus 10 ' unsaturated " yolks per day	2 wk	244	165
Low-fat basal	10 days	195	128
Basal plus 10 plain yolks per day	2 wk	250	179

Although no striking differences were seen between the " unsaturated " and ordinary eggs, the rapid rise in cholesterol levels which ensued when subject 1 received ordinary eggs (return to control values in 4 days) and the high final cholesterol levels in subject 2 might be significant. Accordingly, a trial using formula diets was carried out.

Formula diets —The formula base is that described by Beveridge et al [3] Egg yolks were added to supply 40% of the calories from fat. This was equivalent to twenty-four yolks per day or approximately 6 6 g of cholesterol per day The results of two sets of trials using three different subjects in each group are shown in the accompanying figures

Despite a sixfold increase in the di- and tri-unsaturated fatty acids of the yolk, there was no significant difference in cholesterogenic effect, compared with ordinary yolks It should be pointed out that the feeding of sunflower-seed oil to hens does not reduce the cholesterol content of the yolk.[4] Our subjects, therefore, received large amounts of cholesterol (2 75 g per day with ten yolks or 6 6 g per day on the formula diet) Egg yolks are known to have a very potent cholesterogenic effect Equivalent or even much greater amounts of crystalline cholesterol added to the diet have little or no effect on serum-cholesterol levels [5] The possibility therefore exists that this effect of egg yolks could be due to (1) a fatty-acid factor, (2) a phospholipid, or (3) lipoprotein-cholesterol factor

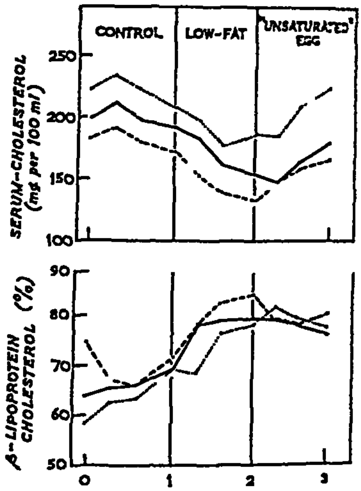

Fig 2—The "unsaturated "-egg formula resulted in a slower rise in serum-cholesterol which did not quite return to control levels in 2 subjects β-lipoprotein cholesterol rose during the low-fat phase and again on the egg-yolk diet

Although the unsaturated-fatty-acid content of our experimental eggs did not approach the optimum ratio postulated by Keys,[6] the changes were substantial enough to have shown some effect if this ratio were crucial It seems far more likely that the hypercholesterolæmia resulting from egg yolk is related to their phospholipid content Corwin,[7] Steiner and Domanski,[8] and Messinger et al [5] suggested that the high " lecithin " content of yolk might be responsible More recently Mustard [9] reported that liver extracts rich in phosphatidyl ethanolamine and containing 0 1% cholesterol produced hypercholesterolæmia and atheroma in rabbits Beveridge [10] reported that the addition of very small amounts of cholesterol to an " inactive " fraction of butter oils restored its cholesterogenic potency The possibility that some specific factor such as a phosphatide might act to enhance the effect of egg-yolk cholesterol would explain our results adequately Eggs are a rich source of phosphatidyl ethanolamine Reduction of the cholesterogenic effects of eggs might therefore be achieved by alteration of the phosphatide content or by a great reduction in the cholesterol content Experiments in this direction are now under way

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Louis Horlick
J B O'Neil

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SEVERE HYPERSENSITIVITY TO SULPHAMETHOXYPYRIDAZINE

SIR,—Discussing this condition in their article of Jan 23, Dr Maher-Loughnan and Dr Tullis say that " Side-reactions are slight and uncommon no serious sensitivity reaction had been reported " They make no reference to similar reactions that have already been reported, and readers may have gained the impression that side-reactions to sulphamethoxypyridazine are relatively rare

This is contrary to accumulating evidence, and I think it may be interesting to recall that in a series [1] of 85 patients taking the drug, reactions occurred in 13 In 1 patient it was a severe generalised bullous and ecchymotic eruption, much like that described by your contributors These and other cases indicate that sulphamethoxypyridazine causes side-reactions in more than 10% of cases, and severe bullous dermatitis seems to be an occasional feature

Edinburgh B K HAREENDRAN NAIR

POLIOMYELITIS A DANGER FOR VISITORS TO NIGERIA

SIR,—From this hospital there has recently been flown to the United Kingdom a young European with poliomyelitis, on a respirator and attended by a medical and nursing team. Three weeks before, a team of doctors and nurses with a respirator had flown to the north of Nigeria to bring this young man into hospital here When he arrived he could move only the muscles of the eyes and lids During the three weeks it has been my privilege to watch the treatment of this young man, which I do not think could have been bettered in any other hospital that I know of When he left here this patient was able to use his facial muscles, could move fingers and toes, and could be independent of the respirator for about four minutes at a time This kind of case is met with not infrequently here, always in Europeans, sometimes the outcome has been less encouraging

Poliomyelitis is virtually unknown in the adult West African, although the late effects of " infantile paralysis " are seen from time to time in children It seems likely that the indigenous population becomes immunised in early childhood as a by-product of the primitive sanitary and overcrowded living conditions That such a state of affairs exists in North Africa is suggested by the studies of Paul and Horstmann [2] and in French West Africa by Said et al [3]

That is one side of the picture Another is that I have seen in the course of work in the medical outpatient clinic here a number of Europeans recently come to this country who have not been inoculated against poliomyelitis While travelling here, by sea, I made inquiries of fellow passengers, quite a number of whom were young adults coming to West Africa to teach or to escape the English winter by visiting relatives here It was a surprise to find that many had not been inoculated Lagos is only twelve hours by air from London and one reads almost daily in the local newspaper of visits of trade delegations and commercial representatives from Europe One wonders whether all these persons realise the risks they may be running

It is possible to get prophylactic inoculation against poliomyelitis in Nigeria but not, of course, as easily as in the United Kingdom The whole question of the inoculation of visitors and temporary residents is to be taken up here with the Federal Ministry of Health In the meantime it cannot be too strongly emphasised that prophylactic inoculation against poliomyelitis should be regarded as essential for any European coming to Nigeria even for the briefest of visits

University College Hospital, HAROLD SCARBOROUGH
Ibadan, Nigeria Temporary Honorary Consultant Physician

THE DIAGNOSIS OF BRUCELLOSIS

SIR,—Your note on my letter last week cannot be allowed to pass without comment for it contains several inaccuracies

You say that of my 35 proven cases 15 were diagnosed by agglutination tests, 2 by skin tests alone, and 18 by a fourfold rise in titre *after* the skin test (your italics) If you read again the table on pages 88 and 89 of the book *Brucellosis in England* you may see that 14 had an initial agglutination titre of 1 in 80 or higher, 2 of 1 in 40, and 4 more of 1 in 20 (Where you got the figure of 15 from I cannot understand) Next there were 14 cases where the skin test was positive 2 of these had already been confirmed by a high agglutination titre, but in 12 (not 2) of them the skin test confirmed the diagnosis That leaves 9 cases only in which the rising titre after the skin test was the sole laboratory evidence of the disease

You also say that you have seen no convincing evidence to justify my interpretation of this phenomenon. May I refer you to the paper by Barrett and Rickards [1] which has now become a classic? They say

> " The results of this investigation would seem to indicate that intracutaneous injection of brucellin in non-sensitised persons does not provoke a significant antibody response, and that a rise in titre of brucella antibodies after brucellin indicates previous or current infection "

Then you depart into the upper regions of fantasy by saying that some of my cases may be psychosomatic and some P U O s Words fail me! It is just because difficult cases have in the past been condemned to such so-called diagnoses that I am fighting this battle P U O (pyrexia of undetermined origin) is not a diagnosis, though many patients present with it. Granted that some of my patients had obscure pyrexia and also proof that they had at some time been infected with brucella surely it is reasonable to assume that there is some connection between the two I hold that it is a reasonable assumption and that in such cases the therapeutic test on which you pour such scorn might well be justified. Now for psychosomatic ailments This diagnosis is popular just now especially in the higher realms of academic medicine, but it is not really a diagnosis, merely a label which explains little We all know that the psyche may affect the soma and vice versa, and never more so than in brucellosis Robinson and Evans [2] say

> " A common feature of chronic brucellosis is the lack of abnormalities to be found in physical examination When the mild symptoms described occur in a patient with no apparent physical abnormality, the picture represents that classified as psychoneurosis "

Harris [3] says

> " The patient with the chronic illness, even though febrile and with demonstrable pathology and positive cultural findings, often presents the picture of radiant health The expression ' You feel so sick but you look so well ' is frequently used by family, friends, and physicians, with the implication that the patient is a psychoneurotic if not a malingerer

And Harris and Kemple [4] conclude

> " The demonstration of psychoneurosis or psychosis is not a sufficient basis for the dismissal of a diagnosis of brucellosis, nor is the converse true They are not mutually exclusive, indeed there may be a definite interrelationship "

I do not feel you are justified in saying " Many physicians will be unconvinced by the diagnosis in at least half the patients" If you had said "Many *pathologists* " I would not quarrel with you In common with most students of this disease I have been trying to press the point made so well by Barrett and Rickards

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[1] Lindsay D G, Prlina I Brichoff, A J, Becker, S W, Sr *A M.A Arch Derm* 1958, 78, 299
[2] Paul J R., Horstmann D M *Amer J trop Med* 1955 4, 512
[3] Said G, Drouhet, V, Soule, J L, Celers J *Bull Soc Med Afr Noir*, 1959, 4, 145

[1] Barrett, G M Rickards, A G *Quart J Med* 1953 22, 23
[2] Robinson F H, Evans A C *J Amer med Ass* 1939 113 201
[3] Harris, H J Brucellosis (Undulant Fever) New York, 1950
[4] Harris, H J, Kemple, C. *Psychosomat Med* 1954, 16, 414

> "We emphasise the fact that the diagnosis of chronic brucellosis *is in the hands of the physician*, and that until some simple and reliable ancillary investigation is elaborated, the results of the clinical examination of the patient should not be obscured by placing too much faith in bacteriological investigation"

Where this advice is not taken cases will continue to be missed It is sad that a journal of your standing should contribute to the perpetuation of such mishaps

Bath HUGH WALLIS

*** As we implied last week we were not certain that we had correctly extracted the information we wanted from the 35 detailed case-histories in Dr Wallis' book, and we are grateful to him for these figures But they do not dispel our doubts about accepting the skin test alone as the sole confirmatory evidence (in 12 cases), and it is hard to see how the passage from Barrett and Rickards' paper, with its reference to "previous or current" infection, answers the questions we raised about the significance of a fourfold rise in titre after injection of brucellin

We assure Dr Wallis that we were not offering "psychosomatic ailments" and P U O as satisfactory diagnoses No-one would deny that some patients whose illnesses remain unidentified under such labels have in fact got brucellosis, and Dr Wallis has done an important service in emphasising this possibility But he will not, we think, on the evidence in his book, persuade his readers—clinicians, pathologists, and others—that he has proved his point in anything like all the cases he records—ED L

FATALITIES AND SPORT

SIR,—*Another rugby football fatality!!!* On Wednesday, Feb 10, a 22-year-old student playing in an intercollege game was knocked unconscious in a tackle and died on Friday after being operated on for a brain injury Do all the fanatical anti-boxing enthusiasts not agree and wish to raise their voices in protest to call for the abolition of this very dangerous and occasionally fatal sport? Or do they on the contrary wish to draw a veil over the incident and continue to regard boxing as the only sport which ever produces death?

London, S W 16 F H TAYLOR

PRIVATE PATIENTS IN THE NATIONAL SCHEME

SIR,—To those who have regarded the denial of free drugs to the private patient as a rank injustice your annotation of Feb 13 comes as an unpleasant shock the arguments sustained therein appear to me devious and of doubtful validity, but as one cannot doubt its essential integrity and freedom from political bias, I, like many others, are prepared to be further instructed

How a private patient not registered on any doctor's list—thereby saving the country a capitation fee—making use of a private doctor's services in any way interferes with the service given by National Health practitioners is difficult to see, and likewise it is difficult to understand how such a doctor is to be regarded as having "entered the Health Scheme" by prescribing to his patient, under proper safeguards, those drugs which are the patient's right, having regard to the latter's contribution, often excessive, to the general body of taxation, out of which the Health Service is maintained

If he does get better service, and this may not necessarily be the case, then the greater is the spur to see that facilities for patient care in the Health Scheme are improved and this tangible criterion is in my view infinitely worth preserving If it was a case of too much money chasing too few goods (doctor's services) a case could be made, but as the supply of doctors is likely to exceed the demand, if present student entry is maintained, no strength is added to the argument on this score

Again reference to the private hospital bed as an "apparent exception" can bring no joy to B U P A and other allied excellent schemes, as these provide for private nursing-home and private hospital bed facilities and for the private services of surgeons and specialists, and if argument as construed in your annotation is to be consistent then these schemes are against public policy This I cannot believe, but if persisted in, I can only draw the conclusion that *The Lancet* is out of step with the views of the thousands of provident and thrifty people who support such schemes

It could, of course, be argued that a doctor having a National Health practice and some private patients not registered with any doctor might be tempted to give a different level of service to the latter, but this surely does him a gross injustice, and in any case the annotation specifically refers to "purely private doctors"

Reference to "buying and selling" medical care merely confuses the issue the fact is that services and drugs purchased with our money should be available to us as of right, and with it the right to make use of them in part or in whole as specifically promised by Mr Bevan, when he became the first Health Minister, and this has been denied with a blatant cynicism which seems to afflict all Governments whatever their political colour

London, S W 1 ROBERT CUTLER

SIR,—It is to be hoped that your annotation will produce more thought and discussion than was shown when this subject was last raised in the *British Medical Journal* in November, 1958 The importance of the issues has been more widely realised in the country now, and despite the Royal Commission report the subject will not lose its importance

Your assessment of the most serious dangers of creating two standards of service in the N H S is much in accord with our own, but since it is a complicated issue and various aspects are stressed we think it right to qualify and question some of your remarks Firstly, the view, widely held by supporters and even some opponents of the proposal to provide drugs for private patients, that there is some injustice, is in our opinion erroneous (We have no strong feelings about Private Practice as the Original Sin of Medicine) It would be an injustice indeed if anyone were refused access to any one part of the National Health Service, but since in fact the Cohen committee—and age-old practice—have held that consultation and prescribing was one item of service, there can be no real grievance Those who wish to avail themselves of the amenities of the Health Service must do so on the same terms as hold for the rest of the country (In fact if you pursue the logic of your argument that having paid once people should not have to pay again, you can gather little solace that the hospital pay-beds are justly run Those paying "full cost of treatment for private beds" are therefore overpaying and are also harshly treated since they have already paid for this part of the service)

Secondly, the attitude of the British Medical Association membership is taken too readily for granted to be *in support* of drugs for private patients The financial and social implications of the proposal are being more widely realised

The main danger is, as you say, two standards of service But you fail to bring out that with the inadequate general practice organisation the N H S would be even further undermanned in actual medical time, and consequently the second standard would necessarily be even lower than already exists. This is adumbrated in your statement that there would be "a vested interest in preserving the defects of ordinary medical care" Sectional interests would thus not only gain privilege but be actually operative in depressing the standards available for the community To establish the " rights " of the few, the " rights " of the many would be jeopardised if not actually sacrificed.

A less easily defined but no less real danger would be the psychological effect on the faith of the country in the N.H S "Nationalised " medicine would be the poor man's medicine Already one often hears " But I'm willing to pay for anything else", in spite of the fact that most general practitioners give their best and there is comparatively little private practice. If this belief spreads it would be as calamitous for the profession as for the patient. We would be divided into the poor doctors, and those who charge The vast majority of general practitioners have their future bound up with the N H S and any disparagement or deterioration of conditions in the Health Service will adversely affect the doctors no less

In addition, the desire to stimulate private practice (an avowed aim of the measure) will largely result in stimulating competition. The cooperation and improved relationship which was noted since the inception of the N H.S and the marked diminution of financial competition will once again increase The weary and slow progress to closer integration amongst general practitioners will be halted and group practice and health centres almost wholly obstructed

Even if the Royal Commission has envisaged possible changes that would be associated with increased private practice, it is doubtful if such a contingency could be fully covered—and would we then have a further inquiry?

The proposal of drugs for private patients is not merely important in itself, but would in fact emphasise and perpetuate some of the worse features that already exist in the N H S In few places in the world is there such a vast expenditure on the training of individual doctors, certainly nowhere do the doctors or the community reap such poor rewards in the exploitation of their skills The main defect of general practice is that it is in fact " Ancient Medicine in Modern Society "—and the rest of the health service organisation is based on the general practitioner[1]

In your leader,[1] Charges for Pay-Beds, you rightly observe "Reform would be a far more popular process if it never removed anything good until it had provided something better" The proposed changes can hardly be said to merit the title of " reform " There are dangers in venturing into the untried in organisation. " Freedoms " and " rights " must not be cast away lightly, but so far in the profession we seem to have traded in the substance for the slogan (In what other circumstances would it be necessary or possible for an outside commercial organisation to set up relief working for doctors ?)

Society can ill dispense with the traditional general practitioner, who has an important contribution to make, but we must devise ways of enabling him to meet his obligations to the community and encouraging him to make the contribution which his special knowledge and quondam skills qualify him The overcrowding and over-waiting in doctors' surgeries, and the overburdening of the doctor himself, will not be alleviated one jot by pressing for this measure

Birmingham B BARNETT
M BARROW

SIR,—Your annotation was so appalling, and so obviously inspired by left-wing bias, that I have decided to cease taking *The Lancet*

For some years now your journal has done its best to produce disunity within the profession My anger with it has been simmering for some time and I have now decided that the time has come for me to register my complaint by cancelling my banker's order

I might add that I run a large working-class practice and that I should probably lose slightly by the fact that my patients will still all remain N H S ones and that the central pool may be reduced if this injustice is put right It does not alter my conviction that it is grossly unjust and illogical to prevent drugs for private patients when these people are allowed their X-rays free, their hospital service free (including drugs!), and their domiciliary visits Why pick on drugs as an exception ?

Space does not allow me to take up your foolish comments on the hospital beds being rented out by the N H.S , your facts are not right here either No doubt in due course I shall read that there has been a take-over bid for your " rag " from the *Daily Mirror*

Shoreham-by-Sea,
Sussex ANTHONY PARTRIDGE

SIR,—I am more than surprised at your assumption that the provision of " free " medicine for private patients would result in two standards of general practice Perhaps I am fortunate in my colleagues in Bristol, but I have not yet met one who gives less attention to his N H S than to his private patients In my own waiting-room nobody can distinguish the one from the other

As private practice keeps up one's standard for *all* patients a doctor will therefore automatically benefit his State patients

Bristol H K V SOLTAU

SIR,—All concerned in improving the standard of general practice will welcome your courageous annotation Like good wine, the National Health Service will grow richer by increasing its own strength rather than by its dilution

London, N W 2 D S NACHSHEN

SIR,—I am surprised that *The Lancet* should indulge in such sophistry as the annotation last week on this subject The so-called apparent exception is an exception indeed The private bed in the public hospital rented at an empirical price enables the patient not only to buy the " personal care " of his consulting attendant but also to enjoy the full benefit of free drugs, dressings, and ancillary care which his attendant can prescribe The statement that payment for personal care within the National Scheme does not exist is only true so far as the general-practitioner service is concerned In practice it is available to any patient who elects to go under the care of a consultant fortunate enough to control private beds

London, W 1 JEROME STURRIDGE

*** To those who believe that medical privileges should not be purchasable within the National Health Service, the defence of private pay-beds in public hospitals can certainly sound a little sophistical We ourselves have continued to defend them on the ground that, so long as they cost the service nothing, they can be said to be outside it. The wish to avoid having different standards of care within the service is not, of course, confined to people of particular political convictions

If the proposal were simply that " purely private doctors " should prescribe N H S drugs, we should be less troubled our objections, though we think them valid, might not be of much practical importance But an N H S doctor prescribing N H S drugs to someone registered with him as a private patient is unquestionably within the Health Scheme, and grave harm would be done if his patients began to transfer from his ordinary list to his private list in the hope of getting something better for a fee It is the amenities of the ordinary list, rather than those for the fee-paying patient, that the N H S has a duty to improve —ED L

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[1] Lancet, 1952, ii, 229

Obituary

ROBERT HUTCHISON

Bt., M D , LL D Edin , Hon D Sc Oxon , LL D Birm ,
Hon M D Melb , F R C P , Hon F R C P E

BEFORE the war we wrote "There can be few men alive today who have had a more intimate influence than Hutchison on the everyday practice of medicine, and he has achieved it largely by the direct impress of personality

"All over the world practitioners think of his precepts as they work at the bedside, their faces faintly reflect his smile as they remember his salted sayings, and they are daily saved from imprudence and humbug because they were taught by a man with a sublime gift for common sense"

Press Portrait Bureau

Twenty-one years later, his influence may have been attenuated by passage, but by those who knew him he will always be remembered not only as one of the great clinicians and teachers of our time, but as a man of individual character Having chosen his role, he played it with the touch of exaggeration needed to make his teaching memorable, and he enjoyed *his prejudices* But the ability, the wisdom, the clinical genius, were very *real* Moreover, the grave and the gay, severity and kindness, were so joined in him that he could raise standards yet be held in general affection

He was born at Kirkliston, Midlothian, and one account of him describes a boyhood classically austere, with excess of oatmeal and a four-mile walk to school Having the kind of early promise *that is later fulfilled*, he was Ettles scholar at Edinburgh University and senior president of the Royal Medical Society, graduating with first-class honours in 1893 In surgery those were still the days of the carbolic spray, and he afterwards recalled that almost his first duty as a dresser was to give an anæsthetic (chloroform) for a long abdominal operation—having never seen one given before

After house-appointments in Edinburgh, he worked in Paris and Strasbourg before becoming demonstrator of chemical physiology in the university In that post, and in 1896 when he took a house-appointment at The Hospital for Sick Children, Great Ormond Street, he produced the earliest of his many papers (a handlist of 276 was compiled by Dr White Franklin in 1951), his first subjects being the movements of the fontanelle, the state of maternal and fœtal blood at birth, estimation of the alkalinity of the blood, degeneration of brain cells, and, particularly, the chemistry and pharmacology of thyroid secretion He had a considerable record of research when in 1897 Leonard Hill invited him to The London Hospital as assistant in the physiology department In the residents' quarters at Great Ormond Street he had already planned and executed with Harry Rainy the first edition of their *Clinical Methods* which remains the guide of so many students, though its editors have changed With so many outstanding qualifications he was elected in 1900 to the staff of The London and also of The Hospital for Sick Children

Describing those far-off times, he has remarked characteristically that "looking back through the mist of half a century, we seemed to get on very comfortably indeed Whether the patients got on as well was, of course, a totally different matter" The wards presented a very different picture from those of today, with diseases generally in more advanced form, and four or five typhoid patients in each ward In the 1900s, he admitted, a medical ward was a rather depressing place, and the children's wards must likewise have been grim. "*Summer*" *diarrhœas*, acute marasmus, and such deficiency diseases as rickets were appallingly prevalent in the East End, with its poverty and ignorance, and Hutchison could have found no more useful interest than nutrition and diet, to which he gave much thought At a time when authorities elsewhere were *complicating* the feeding of infants, he preached simplicity, saying that the infant's response is the only valid test of a feeding plan ("My dear boy, all that you need to know about infant feeding can be written on the back of a postage stamp") By one of his "premonitions", as Dr Langley Porter has called them, he made The London Hospital supply mothers with free cod-liver oil to add to the diluted sweetened evaporated milk which was all that many of them could afford for feeding their babies

In the early years of the century, Hutchison was one of a group of able men at The London who were rejecting the concept of the clinical entity, and, deeply influenced by the biological approach of the German school, were coming to think in terms of maladaptation to environment Arthur Keith and William Bulloch were his intimates, and there were many other stimulating people in the hospital—Leonard Hill, and Henry Head, and H M Turnbull among them (Turnbull used to relate that on their annual departure to the North for Christmas—in separate carriages—Robert attracted much attention as he paced the King's Cross platform in deerstalker cap, a long caped overcoat, and Mother Hubbard boots—the living image of Sherlock Holmes!)

Born to be a teacher, he reacted to his environment by writing further books, some of them in lecture form and several of them astonishingly successful *Hutchison's Food and the Principles of Dietetics*, still a standard work, started life in 1900, and *Lectures on Diseases of Children* in 1904 With Stansfield Collier (and later Reginald Hilton) he edited *An Index of Treatment* from 1907 This was the year in which, as an original member of the editorial board of the *Quarterly Journal of Medicine*, he contributed to its first number his famous paper On Suprarenal Sarcoma in Children with Metastases in the Skull Since 1910, when Homer Wright showed that the cells of these tumours arise from embryonic sympathetic nerve-cells in the medulla, the disease has been called neuroblastoma of the suprarenal medulla (Hutchison's type) In 1908 a handbook on *Applied Physiology* appeared, and in the later '20s it was followed by *Lectures on Dyspepsia*, his London Hospital lectures called *The Elements of Medical Treatment*, and *Some Principles of Diagnosis, Prognosis, and Treatment*

His ward rounds, with Hutchison a formal and often formidable figure in grey frock-coat, have often been described. What was most important about them, for student and houseman, was the sensitive way in which he dealt with patients, old and young, and the delicacy, the economy, and yet the completeness of his examination.

> "To watch him examine an infant, especially one with pyloric obstruction, was an unforgettable lesson in clinical procedure. The gentleness, not only of his manipulations, but also in the spirit of his approach, made one feel that, without sentimentality, the man was alive with sympathy for the suffering child. . . . He made his own demonstrations brilliant examples of what to do, and what not to do, in clinical examinations of the patient."

Again there was the frequent evidence of wide and up-to-date reading, so that new knowledge supplemented experience. Diagnosis and prognosis were brought to a fine art. In his earlier days at The London there were, of course, no reports from X-ray department or biochemical laboratory.

> "You may say 'Well, in that case the diagnosis must have been very often wrong.' There, however, you would be in error. It was not, as a matter of fact, often far wrong. The object of diagnosis fifty years ago was chiefly to tell what would be found post mortem, and in that art the physician with his highly developed clinical instinct was extraordinarily skilful."

Dr Donald Hunter said that of all Hutchison's messages to his pupils this was the greatest—that as Medicine becomes more complicated good clinical method grows rather than lessens in importance.

It would be idle to pretend, however, that only his skill and shrewdness made these occasions memorable: there was also the fascination of watching someone different from anybody else, and listening to his fastidious utterance—fastidious and courteous even in his occasional invective. (Who, as a student, would not enjoy Hutchison's description of his Great Ormond Street clerks as "a curious collection of crapulous cretins creeping from crib to crib", or the comparison of his London Hospital ones to tabetic snails?) Like all good teachers, he took trouble to make his point memorably: when a certain type of squealing, kicking baby came into the outpatient department he would ask, "What is the treatment here?" and getting no answer would say, "Gentlemen, it is a clear-cut case of bromide for the mother." His lectures are full of pearls (as he would not scruple to call them):

> "It is quite impossible that you should always be right in your diagnosis, if only for the reason that disease does not always play the game. It is better, however, to be wrong on sound principles than right by chance. Guessing is to be avoided at all costs, for if once you get into the habit of guessing you are diagnostically damned."

He believed in what some character in *The Wrong Box* calls "judicious levity"—a phrase that came beautifully off his tongue. Urging that nobody should ever start a lecture in his memory, he remarked: "There are better ways of commemorating the dead than by boring the living."

Naturally he himself was asked to give many lectures, including, at the Royal College of Physicians of London, the Goulstonians of 1904 and the Harveian oration of 1931. He was elected president of the college, in succession to Lord Dawson, in 1938, having previously been president of the Association of Physicians and of the Royal Society of Medicine. His scholarship and distinction of mind earned him the highest honours that Medicine can bestow, but in spirit he was neither an administrator nor a man of action and his main achievement was not in such offices. He was created a baronet in 1939 and spent the last part of his life at his home at Streatley-on-Thames. Even during his active years he had been a good deal disabled by a longstanding disorder. "Still," he wrote, "as a disease it has two great merits: (1) it is entirely painless, (2) there is no known treatment. I am therefore spared all modern therapy."

We conclude with a note from W. R. B.:

> "Robert Hutchison's character was so complex that almost anything which it seems obvious to say about him needs qualification. He became a doctor before X rays were discovered, and retired from his hospitals at the beginning of the 1930s, before the major therapeutic discoveries of that decade had been made. An exponent of medicine as an art rather than a science, and a brilliant intuitive diagnostician, he had more in common with the 18th century than with the middle of the 20th. He was almost the last of a kind of physician now nearly extinct. Yet his early contribution to dietetics was scientific, and at heart he was far more of a scientist than he allowed his students to know.
>
> "I am not sure whether he invented the classification of doctors into 'winduppers' and 'pooh-poohers', but I have heard him use it. He himself was a 'pooh-pooher' on the largest scale, but this, one felt, was a public persona which he had constructed by elaborating some of his native characteristics. Fortified by his gaunt and lanky appearance, his slow and dignified gait, a grey frock-coat, his Edinburgh accent, and his wit, it was a formidable facade, which might have made him admired and even a little feared. Yet he inspired, particularly in his colleagues and pupils, an affection which earned him the improbable diminutive, Bobbie. Relaxing in the staff-room after a ward round, he would put off the persona as far as he could, address one as 'My dear boy', and chuckle over some anecdote which was 'really very amusing'. Behind the mask there was, I think, a rather shy and lonely man, who, like an ancient Stoic, found life on the whole a bad thing one had to make the best of."

Another of his friends once put forward the opposite conclusion, saying that the pessimism was the mask, and behind it was a mind intellectually gay, with a cordial distaste for the dull. Both views could be sometimes right, for it was his complexity that made him so interesting a person.

Sir Robert Hutchison died at his Berkshire home on Feb. 12, aged 88. He married, in 1905, Lætitia Norah Moore-Ede, M.B. Lond., daughter of the Very Rev. Dr. Moore-Ede. Lady Hutchison survives him with two sons and a daughter. Mr. Peter Hutchison succeeds to the baronetcy. Sir Robert's brother, the late Sir Thomas Hutchison, was Lord Provost of Edinburgh in 1921-23.

In preparing this memoir we have drawn gratefully, though usually without acknowledgment, from tributes which appeared in the *Archives of Disease in Childhood* in October, 1951, and in the *London Hospital Gazette* at various times.

WALTER PATON MacCALLUM

C.B.E., D.S.O., M.C., E.D., M.B. Sydney, F.R.A.C.P.

Dr. MacCallum, consulting physician to the Prince Henry Hospital, Sydney, died on Nov. 22. He had held office in the Royal Australasian College of Physicians as honorary secretary from 1948 to 1950 and as honorary treasurer from 1950 to 1958.

During the 1914–18 war he served in the infantry and staff of the Australian Imperial Force in Gallipoli, Egypt, France, and Belgium and was awarded the M.C. and D.S.O. He was demobilised in 1919 with the rank of major, and returned to Australia to study medicine at the University of Sydney, and the rest of his medical life, apart from further war service, was spent in that city After qualifying in 1924 he held house-appointments, and in 1926 he joined the staff of the Royal Alexandra Hospital for Children In 1934 he was also appointed to the staff of the Royal Prince Alfred Hospital During the late war he served with the A A M C from 1940 to 1947 in Palestine, the Western Desert, Greece, Crete, Netherlands, East Indies, and the South-West Pacific In the later years of the war he acted as deputy director-general of medical services with the rank of brigadier, and for this work he was appointed C B E

He was elected F R A C P in 1946, and his published work included papers on rheumatic fever and meningitis in childhood '

A colleague writes

" MacCallum belonged to one of the outstanding families in New South Wales, and had, himself, a first-class mind and an attractive manner He was one of the group of senior physicians who guided the Australasian College along sound lines in its early critical years "

JAMES IGNATIUS ENRIGHT

B A, M D R U I

Dr J I Enright died on Jan 13 in Dublin In the 1914–18 war he took part in investigations on pellagra among prisoners-of-war in Egypt

He was educated at a Jesuit College and the Royal University of Ireland He graduated M B with honours in 1914 After holding resident appointments at the Eastern Fever Hospital, Homerton, and the Royal Sussex Hospital, Brighton, he became medical officer in charge of a prisoner-of-war hospital in Cairo On his return to Ireland he settled in practice at Dalkey, where he was born

P H M-B, who worked with him in Cairo, writes

" Enright was then a young, impulsive, loquacious, and witty Irishman with an inquiring mind Among the wretched, emaciated, and half-starved Arabs and Turkish prisoners he found much to interest him Pellagra had just made its appearance in many strange and unforeseen guises, and he became familiar with pellagra typhus, and many peculiar actinogenic eruptions on the face, hands, and legs, as well as œdematous swellings Later he reported these observations and also an equally instructive outbreak of pellagra in the seemingly well-fed and nourished Austrian and German prisoners during 1917 and 1918 (The paintings which were made for him by an Austrian sergeant, who was by trade a sign-painter, are now in my possession) He also described an unrecorded fatal urinary infection with *Bacterium coli* which was traced to miliary cortical abscesses in the kidneys

" Ignatius was a fluent and entertaining speaker, with a delightful brogue, and he could quote at length from Latin and English literature Warm-hearted and generous he was a staunch and loyal friend, and his sudden, unexpected eruptions into the metropolis were always welcome "

DR WU LIEN-TEH

W C W N writes

" Wu Lien-Teh was a remarkable man for he was able to enjoy the best of both worlds—the East with its wisdom and the West with its scientific practice He held fast to the traditions and philosophy of his forebears despite the many years he spent in Europe and the United States

" I have reason to be grateful to him for his advice and kindness when I found myself, an occidental, in the orient We had a common interest in that we graduated from St Mary's Hospital, and when he visited Hong Kong he would reminisce on his happy student days at Cambridge and in London He was ever grateful for the friendship of Sir Zachary Cope and Prof T R Elliott

" Most of us start contemplating retirement after the age of 60, but not Wu Lien-Teh I travelled with him and his family in 1937 from Hong Kong to Singapore after the Japanese had overrun Shanghai His beautiful home and valuable collection of ancient Chinese medical books had been burnt I recall his fervour when he said 'I am 60 and have lost everything but I shall not give up medicine I shall open a dispensary in Malaya ' Ironically he was to suffer from the Japanese again a few years later when they occupied Malaya Undaunted he started to practise again after their defeat

" He more than any other Chinese, laid the foundations of a modern medical service for his country It is fortunate that posterity will have in his autobiography—*Plague Fighter*—a record of the achievements of this great doctor "

DR EILEEN HICKEY

P F writes

" Several generations of students of the Belfast School of Medicine were well acquainted with Dr Hickey's tireless energy in social, religious, and political fields, but it is as a *clinical practitioner, teacher, and adviser that she will perhaps* longest be remembered

" As a clinician she was infinitely patient and painstaking, shrewd and wise Her experience extended over four decades of change, *and she could accept with equanimity the encroaching* tide of medical advance, with its bright if rather brittle purveyors of the ' scientific approach ', absorbing the principles *as a good doctor should, but never losing her* sense of perspective The student body were ever her particular concern their deportment, manners, dress—little escaped her vigilance, *and on their application and training* she often expressed herself strongly Her clinical clerks usually found that she did not suffer fools gladly, but they left her firm richer and wiser for the experience

" For some time she had been troubled by a partial deafness, but this affliction only sharpened her clinical acumen 'Had I my way,' she snorted to a student, advancing on a patient whilst *producing* the inevitable stethoscope, ' that instrument would be banned during your first clinical year then perhaps you would use your eyes! ' Or again ' We *make mistakes*, not because we don't know, but because we don't look ' She looked and saw her patients, as well as their illnesses, she saw *her* students as *beginning an odyssey*, she saw her profession in its nobility, and her life as an opportunity to serve "

Public Health

Infectious Diseases in England and Wales

Disease	Week ended January 2	9	16	23	30*
Diphtheria	6	5	3	6	8
Dysentery	728	810	781	861	1092
Encephalitis					
Infective	1	3	1	3	2
Postinfectious		1		2	2
Food poisoning	182	134	139	192	183
Measles, excluding rubella	1501	1107	1049	1069	1790
Meningococcal infection	23	19	20	18	27
Ophthalmia neonatorum	21	16	16	32	19
Paratyphoid fever	9	7	2	1	4
Pneumonia primary or influenzal	373	420	337	311	430
Poliomyelitis					
Paralytic	7	2	10	4	5
Non paralytic	3	2	2	1	1
Puerperal pyrexia	156	189	179	196	231
Scarlet fever	1162	802	933	1189	1775
Smallpox					
Tuberculosis					
Respiratory	396	399	416	419	373
Meninges and C N S	4	3	3	7	4
Other	37	51	48	48	46
Typhoid fever	1	2			1
Whooping cough	521	675	740	884	[illegible]

* Not including late returns

Parliament

Scottish Mental Health Bill

On Feb 9, in introducing this Bill, which has already been briefly described in our columns,[1] Mr JOHN MACLAY, Secretary of State for Scotland, said that it had three main threads, to retain the best features of the existing law, to weigh the balance wherever there was doubt in favour of the liberty of the subject, and to devise a code which was in harmony with authoritative medical opinion.

Miss MARGARET HERBISON welcomed the Bill on behalf of the Opposition with two reservations She regretted that responsibility for the training and occupation of the so-called "ineducable" children should be transferred from the education to the health authorities, and she was uneasy that the local authorities' powers to provide community mental-health services were only permissive and not mandatory These new services would place a heavy burden on the authorities and she asked what financial help would be given to them.

Uncertainty about the local-authority services was a recurrent theme in the debate (which was interruped for three hours for a discussion on the breakdown of the Cyprus talks) Mrs JUDITH HART pointed out that the authorities already had most of the powers necessary to give community care to the mentally ill and the mentally defective, but made disappointingly little use of them. For instance, out of 49 Scottish county councils and large boroughs only 1 had appointed a special committee to deal with mental health Too few child-guidance clinics had been provided, and those that existed often had no consultant psychiatrist or psychiatric social worker on the staff There were only 2 senior medical officers in Scotland engaged wholly in mental-health work. Of the 118 welfare and mental-welfare workers in the Scottish counties 70 were also district clerks, and probably only half their time could be given to their mental-welfare duties 5 psychiatric social workers were employed in the whole of Scotland, but not all 5 were fully qualified. Mental-health work would not progress until the authorities' powers were translated into duties

Dr J DICKSON MABON suggested that if the Government persisted in their present attitude towards finance we should be no better off with the passage of the Bill. For twelve years the local authorities had had permissive powers, and the Secretary of State had been able at any time to direct that they should become duties Yet the Fyfe Committee had severely criticised the administration of the mental-defective service in 1957 and precious little had been done since

Mr T G D GALBRAITH, joint under-secretary of State for Scotland, said that the Bill set the legal foundation for the things to be done in terms of care, treatment, and aftercare. It did not itself provide the accommodation or recruit the workers These services were all the responsibility of various agencies, and the Bill laid down only the law under which they would work. Therefore, it did not require substantial new charges They looked to the local authorities to play a large part in the expansion of the mental services outside the hospitals and within the community The expansion would certainly involve considerable expenditure, and he assured the House that it would be taken into account in the discussions on the general grant for local authorities which would be held later this year He recognised that this arrangement did not altogether satisfy all hon. Members and that there might be differences of opinion as to the best way of financing local-authority services

There were several reasons, he continued, against making the local authorities' powers permissive rather than mandatory Not all authorities had the same potential for expansion, and any statutory duty would therefore have to be limited to what the smallest authority could manage If local democracy was to mean anything authorities must at least be given the chance to exercise initiative Again for the rest of the health service the authorities' powers were permissive, and the Government was anxious that the mental and physical health services should be treated in the same way Dr MABON pointed out that the mental-health services were not at the same stage of development as these for physical health But Mr GALBRAITH maintained that we must have permissive powers for both at a time when we were trying to make the two types of medicine comparable

QUESTION TIME

A Seat in the Cabinet?

Mr L A PAVITT asked the Prime Minister if, in view of the negotiations with the medical profession following the publication of the report of the Royal Commission on Dentists' and Doctors' Remuneration and the importance of the Government's decisions arising therefrom, he will enlarge the Cabinet by the inclusion of the Minister of Health Mr R A BUTLER replied The hon Member would be wrong if he thought that, because the Minister of Health is not a member of the Cabinet, the Government will give less than due attention to the questions raised by this report. Mr PAVITT Will the Leader of the House urge the Prime Minister to take into consideration, not only the Government's position *vis-a-vis* the Minister, but, in view of these negotiations with the medical profession, the need for confidence on the other side in the negotiations if the outcome is to be satisfactory? The report may well set the pattern of the family doctor service for the next twenty years The way in which previous negotiations were carried on destroyed the confidence of the medical profession This single act perhaps would be sufficient to restore confidence in the Government. Mr BUTLER The hon Member's question will have done a service if it draws attention to the fact that the Government attach the greatest possible importance to this Commission and to the findings I can assure the hon Member and the House that this matter will be treated by the Government as one of the first importance

New Drugs

Mrs HARRIET SLATER asked the Minister of Health what proposals he had for controlled research and testing of new drugs before they were sold without a doctor's prescription —Mr DEREK WALKER-SMITH replied While there are powers which enable supply to be permitted only on medical advice and prescription there is no authority under existing legislation for this requirement. The Committee on the Cost of Prescribing has, however, made a recommendation that all new drugs should be subjected to clinical trial, and I hope soon to be able to reach a decision on it.

Drugs for Private Patients

Dr DONALD JOHNSON asked the Minister what undertaking was given by the British Medical Association, in making its representations to him last year about the desirability of supplying drugs under the National Health Service to private patients, to cooperate in the administration of safeguards against over-prescribing on the part of private doctors —Mr WALKER-SMITH replied In discussions with officers of my department on the possibility of making the kind of financial and administrative arrangements which would be required if it should be decided as a matter of policy to introduce legislation, the Association agreed to safeguards on similar lines to those applying under the National Health Service

Sabin Oral Vaccine

Mr W G CLARK asked the Minister whether it was intended that there should be trials of Sabin oral poliomyelitis vaccine in this country —Mr WALKER-SMITH replied The Medical Research Council will shortly be carrying out small-scale trials of this vaccine in selected areas and I am asking the local health authorities concerned to give their full cooperation

Employment of Disabled

Of the 695,000 registered disabled just under 60,000 were registered as unemployed in January

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[1] See *Lancet*, Jan 30 1960 p 290

Control of Drugs

The Poisons Board have recommended that the following substances, as well as 'Preludin', should be made available only on medical prescription

- Acetylcarbromal
- *Androgenic and œstrogenic substances, the following
  - Benzœstrol
  - Steroid compounds with androgenic or œstrogenic activity, their esters
  - Derivatives of stilbene, dibenzyl or naphthalene with œstrogenic activity, their esters
- Azacyclonol, its salts
- Benactyzine, its salts
- 3-Benzylhydrazinocarbonyl-5-methyl*iso*oxazole, its salts
- Bromvaletone
- Captodiame, its salts
- Carbromal
- 2-*p*-Chlorophenyl-3-methylbutane-2 3-diol
- Guaiphenesin
- 4-Hydroxymethyl-2 2-di*iso*propyl-1 3-dioxolan
- Hydroxyzine, its salts
- Imipramine, its salts
- Mephenesin, its esters
- Meprobamate
- Metformin, its salts
- Methocarbamol
- α-Methyl-phenethylhydrazine, its salts
- *Methyl phenidate, its salts*
- Nialamide, its salts
- Phenelzine, its salts
- Phenformin, its salts
- Pipradol, its salts
- Rauwolfia, alkaloids of, their salts
- Thalidomide, its salts
- Zoxazolamine, its salts

* Except preparations intended for use in external applications and animal feeding stuffs

Medicine and the Law

Probation for Schizophrenic

An 18-year-old youth, who pleaded guilty to stealing over £15,000 from the city treasurer's department at Norwich whilst employed as a clerk there, has been put on probation for three years [1]

Dr William Abel, of Hellesdon Hospital, said in evidence that the youth was a typical schizophrenic The prison medical officer, Dr B M Tracey, agreed with most of Dr Abel's findings

In putting this offender on probation, Mr Justice Byrne said " You have pleaded guilty to an extremely serious offence which would merit many years of imprisonment in normal circumstances But two doctors agree that you are mentally ill If I sent you to prison, you would probably become a criminal "

It is a condition of the probation that he goes to a mental hospital for twelve months

No Home for an Epileptic

The policy of the courts in dealing with first offenders is to avoid giving a prison sentence unless this is clearly indicated by the seriousness of the offence or for some other reason It is strange, therefore, that the Nottingham magistrates should have found that they had no option but to remand a pregnant woman suffering from epilepsy to prison for three weeks for what may be described as welfare reasons

The woman, aged 27, had pleaded guilty to stealing £12 10*s* from a wallet in a shop [2] She took the money, handed the empty wallet back to the owner, and later took most of the money back and said she had spent £1

On her third appearance in court, it was reported that four epileptic colonies had refused to have her because of her pregnancy, and a mother-and-child home had refused to have her because she was considered unstable in view of the epilepsy Her husband had been sentenced to two years' imprisonment three days after they married

Ordering that the case should be sent to the Home Secretary, the chairman of the bench said that there had been " a grave lack of responsibility on the part of certain branches of the medical services " Remanding the woman to prison was the only way of ensuring that she received proper medical attention

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[1] *Guardian*, Feb 11, 1960
[2] *Guardian* Feb 13, 1960

Diary of the Week

FEB 21 TO 27

Monday, 22nd

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P.M Dr Brian Ackner Attempted Suicide
GUY S HOSPITAL, S E 1
5.30 P.M Prof W J H Butterfield Diabetes Mellitus
HUNTERIAN SOCIETY
8.30 P M (Mansion House, E.C.4) Mr C. R. Rudolf New Light on William Clift and His Contemporaries. (Hunterian oration.)
MANCHESTER MEDICAL SOCIETY
9 P.M (Medical School, University of Manchester) *General Practice* Dr M C G Israels Pitfalls in the Diagnosis and Management of Blood Diseases
UNIVERSITY OF ST ANDREWS
4 P.M (Queen s College, Dundee.) Dr H B Goodall, Dr William Walker Megaloblastic Anæmias

Tuesday, 23rd

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P.M Prof D E Denny-Brown Diseases of the Basal Ganglia and Their Relation to Movement (First of two Croonian lectures)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P.M *Medicine* Dr Graham Hayward, Dr Mary Barber, Dr John Goodwin Bacterial Endocarditis
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M (London School of Hygiene and Tropical Medicine, Keppel Street, W C.1) Dr W R S Doll Epidemiological Methods in Leukæmia Research
INSTITUTE OF DERMATOLOGY, Lisle Street, W C.2
5.30 P.M Dr S L Szur Radiotherapy in Dermatology
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C.1
5.30 P.M Mr Kenneth McLay Tests of Acoustic Function (I)
MANCHESTER MEDICAL SOCIETY
4.30 P.M (Medical School, University of Manchester) Dr J N Mills J S Haldane (University lecture)
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P.M *(General Infirmary at Leeds) Dr J A Sharp* The Rhinencephalon.
UNIVERSITY OF ST ANDREWS
5 P.M (Queen's College, Dundee) Prof R. E Coupland Basic Methods in Histochemistry

Wednesday, 24th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M Dr A E Mourant Significance of Human Blood-group Distribution
INSTITUTE OF DERMATOLOGY
5.30 P.M Dr R W Riddell Laboratory Diagnosis of Mycotic Lesions.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W.3
5 P.M Dr Paul Wood Chronic Constrictive Pericarditis.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5 30 P.M Mr McLay Tests of Acoustic Function (II)
MANCHESTER MEDICAL SOCIETY
4 30 P.M (Medical School, University of Manchester) *Medicine* Dr R W Luxton The Common Health. (Presidential address)
UNIVERSITY OF ST ANDREWS
4 P.M (Queen s College, Dundee) Dr H B Goodall Hæmolytic Anæmia in Pregnancy

Thursday, 25th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M Professor Denny Brown Diseases of the Basal Ganglia and Their Relation to Disorders of Movement. (Second of two Croonian lectures)
UNIVERSITY OF LONDON
5.30 P.M (Royal Free Hospital School of Medicine, 8, Hunter Street, W C 1) Dr Sybil Cooper Relations Between the Histology and the Physiology of Muscle Stretch Receptors
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M (London School of Hygiene and Tropical Medicine.) Prof. Sheila Sherlock Liver Failure
INSTITUTE OF DERMATOLOGY
5.30 P.M Dr F Ray Bettley Lupus Erythematous
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5.30 P.M. Mr McLay Tests of Vestibular Function (I)
MANCHESTER MEDICAL SOCIETY
8 P.M (Staff House, University of Manchester) *Anæsthetics* Dr Tom Dinsdale, Mr G V Ashcroft, Dr W Ken Jones Dental Anæsthesia
UNIVERSITY OF ST ANDREWS
5 P.M (Queen s College Dundee) Prof A C Frazer Diagnosis, Pathogenesis, and Treatment of Defective Intestinal Absorption.

Friday, 26th

ROYAL SOCIETY OF MEDICINE
5 P.M *Pædiatrics* Dr Mary Sheridan, Mr Gavin Livingstone, Mr Michael Reed, Miss W Galbraith Hearing and Speech Disorders in Childhood
8 15 P M *Obstetrics and Gynæcology* Mr V B Green-Armytage, Mr M D Arwyn Evans, Mr D S Perchard Hypnosis in Obstetrics and Gynæcology
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Professor Sherlock Diagnosis and Treatment of Portal Hypertension
4 P.M Dr Fraser Roberts Medical Genetics
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
5.30 P.M Mr McLay Tests of Vestibular Function (II)
INSTITUTE OF NEUROLOGY, National Hospital Queen Square, W C.1
4.30 P.M Dr John Foley Hypertonus and Hyperreflexia
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street W 1
7.30 P.M. Dr G L. McElligott Venereal Disease and the Public Health

Notes and News

EFFECT OF RADIATION ON HUMAN HEREDITY

IN some widely scattered areas of the world the level of atural background radiation is well above that in other parts f the world, and properly planned studies of the populations n such areas could make significant contributions to knowledge f the genetic and somatic effects of prolonged exposure to w levels of radiation. The recent report[1] of the W H O xpert committee on radiation surveys the known areas of igh background radiation and sets out the principles of lanning investigations of such areas The Kerala area, at the outhernmost extremity of the west coast of India, is probably he only area now known which might be profitably investiated, and the last part of the report is devoted to the applicaion of the general principles to the planning of what is called "the Kerala project"

Comparison of specific mutant phenotypes in the irradiated nd control populations will rarely be feasible, and reliance ill usually have to be placed on a comparison of populations ith respect to those characteristics that are assumed to reflect he cumulative effect of mutation at many loci The committee nake a number of suggestions concerning information to be ollected in the Kerala project, with particular reference to the d-hoc census that would have to be the first step, and a brief ection of the report is devoted to the estimated requirements n men and material

HOSPITAL PLANNING AT WOLVERHAMPTON

THE Birmingham Regional Hospital Board and the Wolverampton Hospital Management Committee have been onsidering plans for the expansion of hospital services in the Volverhampton group A scheme has been proposed by which he number of beds at the Royal Hospital will be reduced to bout 250 and the hospital will become a centre for casualties nd outpatients on the lines of a policlinic with some inpatient eds The orthopædic department and some orthopædic beds vill remain and other services will include radiology, physioherapy, and pathology A new radiotherapy department will e added, with a cobalt unit and isotope and physics department. There will also be some radiotherapy beds in the main block. The 4 new operating suites, which are at present being designed, will be retained and there will be some beds for the following horacic surgery, neurosurgery, plastic surgery, the burns unit, utpatient investigations, and dentistry and orthodontics The main inpatient service will eventually be moved to the site at New Cross, where it is proposed to adapt six wards to provide an acute admission and rehabilitation geriatric unit, and to build a new maternity unit. It is also planned to build on this site a mental hospital with 350 beds and a new general hospital Once these new buildings are erected some of the smaller hospitals and units of the group, some of which are uneconomic, can be closed.

LIPIDS AND ARTERIAL DISEASE

FEW medical men find time to study Professor Hilditch's large book on *The Chemical Constitution of Natural Fats*, which is a standard reference work for chemists, but now, with Dr Jasperson, he has produced a small monograph[2] which can be strongly recommended for those with only an evening to spare It contains a clear account of the distribution of fatty acids in Nature, and also of *cis-trans* isomerism—aspects of organic chemistry that most medical students in the past have skipped with impunity Nowadays, without some accurate knowledge of these subjects, it is impossible for a doctor to discuss critically with a patient the latest piece of dietary advice for those with ischæmic heart-disease. This summary by Professor Hilditch and Dr Jasperson is a first-class piece of teaching, suitable for both undergraduates and postgraduates

SCIENTIFIC RESEARCH IN SCHOOLS

THREE years ago the Royal Society set up a committee on scientific research in schools, with Sir Lindor Brown as chairman Its second report shows that last year 48 schools were doing research under its auspices, receiving over £2000 in grants All projects are carried out with the specialist advice and assistance of fellows of the society and of others who act as advisers The committee "has been much stimulated by the continued and growing response to this scheme" and looks forward to receiving further requests from schools

EQUIPMENT FOR THE DISABLED

THE National Fund for Poliomyelitis Research is sponsoring a reference book entitled *Equipment for the Disabled*, and it is hoped to publish it in August.

The book will be in loose-leaf form to allow later additions and deletions, and on each separate sheet there will be a photograph, written description, and, where necessary, working drawing of the apparatus

The work of collection and preparation of material for publication is being carried out at the Nuffield Orthopædic Centre, Oxford, by Dr Margaret Agerholm, with the collaboration of Miss E Hollings and Miss W Williams, and she will be grateful for suggestions from colleagues for the inclusion of special apparatus which they have found useful.

INCREASES IN SERVICE PAY

THE increases in pay for those in the Services, announced last week,[1] affect medical officers as follows

Rank (Army only)	*Annual basic pay when first appointed*	
	Old	*New*
	£	£
Lieutenant	657	730
Captain	766	839
Major	1295	1387
Lieut.-Colonel	1660	1806
Colonel	2080	2244
Brigadier	2354	2573
Major-General	3029	3285
Lieut.-General	3759	4124

Retirement benefits have also been improved.

University of Cambridge

Dr E H R. Ford has been appointed lecturer in anatomy and Dr R. H Adrian lecturer in physiology

Royal College of Surgeons of England

AT a meeting of the council on Feb 11, with Sir James Paterson Ross, the president, in the chair, Prof John Bruce was admitted and Prof Carl Semb (Oslo) elected to the honorary fellowship, and the honorary medal of the college was awarded to Sir Cecil Wakeley, past president.

Mr J D T Jones, Mr R. G Macbeth, and Mr A G Cross were admitted to the court of examiners Dr Cuthbert Dukes was appointed Thomas Vicary lecturer for 1960, and a Hunterian professorship was awarded to Mr P M Weston (West Indies) Dr Bertram Cohen was appointed the first Nuffield research professor of dental science and Dr G V R. Born Vandervell professor of pharmacology

The following were elected to the fellowship *ad eundem*

Isabella Forshall, P G Cutlack Martin, G E Moloney, A W Kay

Diplomas of fellowship in the Faculty of Anæsthetists were granted to the following

K W Dodd, G B Burchell I M Brown, T K Hardy, N H Eve, M R Milne, William Braude, W S Dykes J N Thorpe, I W Davidson Sohrab Rustomji Umrigar R D Davie, Nasir Husain Jafry, P W McCormick Mary F West, Catherine K Adam, Gordon Clarke D T McClements, Marie M Simpson, W J Colbeck, Winifred E Elesh, C J R Elliott, J P N Hicks, A B Lodge, W N C McCleery, Norman McLeod D D Moir, E D T Ross, P A Tsoi-A-Sue D M Davies, G C Fisk, Dorothy E Harris, D D Hart, P J W Knell, I M J Mair, R R Manning, Isobel Spears, Lakshman Tisse Wijeyaratne F B N Clarke, A T R Fuller, C F Hider, B A Lyder, Maung U Win, J H Stevens, T H Taylor, R J Thomson

Licences to practise and the diplomas mentioned in our issue of Feb 6 (p 344) were conferred jointly with the Royal College of Physicians In addition a licence to practise was conferred on Patricia S Stephenson and the D.M R.T was conferred on D S Andrew and K D Neddy

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[1] *World Hlth Org tech Rep Ser* 1959, no 166 Pp 47 1s 9d Available from H.M Stationery Office P O Box 569 London S E.1

[2] Lipids in Relation to Arterial Disease a summary of current biochemical evidence. By T P Hilditch, D.SC. F R.I C. F R.S., and H Jasperson, PH.D F R.I C. Pp 39 Obtainable from J Bibby & Sons Ltd., King Edward Street, Liverpool, 3

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[1] Service Pay and Pensions Cmnd. 945 H.M Stationery Office. Pp 40 2s

University of Aberdeen

The following appointments have been made

Dr A H C *Sinclair-Gieben, senior lecturer in mental health,* Dr N G Fraser, *lecturer in mental health,* Dr D C Burke, *lecturer in biological chemistry*, Dr John Findlay, *lecturer in anatomy*

Royal College of Physicians of London

Dr J D N Nabarro will give the Oliver-Sharpey lectures on *Tuesday and Thursday, March 8 and 10*, at 5 P M, at the college, Pall Mall East, S W 1 He will speak on the pituitary and adrenal cortex in general medicine

University of Birmingham Medical School

Prof J Z Young will give the William Withering lectures on Monday, Tuesday, and Wednesday, May 2, 3, and 4 He will speak on mechanisms of learning and *form discrimination* On Wednesday and Thursday, May 18 and 19, Sir Dugald Baird will give the Ingleby lectures He will speak on the evolution of modern obstetrics All the lectures will be given at 5 P.M at the Medical School, Birmingham, 15

Horder Memorial Trust

The trustees of this memorial to Lord Horder have decided to offer a travelling fellowship every third year, of the value of £600, to enable a senior member of the *medical profession* to visit Commonwealth countries It is also hoped that he will give a lecture at St Bartholomew's Hospital or the Royal College of Physicians The first appointment is likely to be in 1961 It is not proposed to advertise the fellowship but the trustees will appoint a selection committee early in October The secretary of the Trust is Dr E M Darmady, Central Laboratory, Milton Road, Portsmouth.

Rockefeller Foundation

During the fourth quarter of 1959 the Foundation made *grants of over $12 million Those for medical and natural* sciences amounted to nearly $6 million These included a three-year appropriation of £24,000 (about $69,000) to the London School of Hygiene and Tropical Medicine for investigations into protein malnutrition

At the school's *human nutrition laboratory* and at the human nutrition research unit of the Medical Research Council the protein content of *tropical foodstuffs is being studied* By experimentally producing in animals two of the severe types of protein malnutrition *which occur in man, it has proved possible to bio-assay vegetable* proteins for the prevention and cure of protein deficiency A technique *for expressing in quantitative terms the protein values of foods* consumed by man has been developed and is being used to establish *requirements of the aminoacids essential to growth and health* The supplementation of deficient diets with vegetable protein sources, such as legumes, *leaf proteins,* and *flour residues, is also* being investigated

The Doctors' Window in Guildford Cathedral

At a meeting of the Guildford division of the British Medical Association last week, Dr G I Watson, chairman of the Doctors' Cathedral Window Fund, handed a cheque for £1000 to the secretary of the Guildford New Cathedral Council

The Society of Apothecaries contributed 55 cheques totalling £268 and the B M A £105 centrally with a further £40 from the Surrey divisions £143 was contributed by medical staffs of London teaching hospitals, while gifts from other corporate bodies totalled £104 Donations from 352 individual doctors at home and overseas amounted to £642

Miss Moira Forsyth, the artist who made the window, was thanked on behalf of the *medical profession* by Dr S Keys, chairman of the division The stained glass panels are now on display at the cathedral

Laboratory Animals Centre

This centre will hold a congress at the University of Nottingham on Monday and Tuesday, April 11 and 12 A symposium on the provision of animals for cancer research will be held at 1, Wimpole Street, London, W 1, on Monday, May 23 Further particulars may be had from the secretary of the centre, M R.C Laboratories, Woodmansterne Road, Carshalton, Surrey

Medical War Relief Fund

During 1958–59 six educational grants amounting to £984, and seven maintenance grants amounting to £710, were made During the past year repayments of £1000 have been made

Biometric Society

This society will hold a symposium in Leyden from May 10 to 13 on quantitative methods in pharmacology Further information may be had from Mr H de Jonge, department of statistics, Nederlandsch Instituut voor Praeventieve Geneeskunde, Wassenaarseweg 56, Leyden, The Netherlands

Community Care of the Mentally Handicapped Child

The Metropolitan region of the National Society for Mentally Handicapped Children will hold a conference on this subject at Church House, Westminster, S W 1, on Saturday, March 12, at 2 45 P M Further particulars may be had from the hon. secretary, Mr E R Skoyles, 194, Kenmore Avenue, Kenton, Middlesex

Mental Patients and the Disabled Register

Regulations made last year have removed the automatic bar to the admission to this register of all patients in mental hospitals or institutions These patients are now eligible for admission, *provided they are able to work,* even though they still remain in hospital This change was recommended by the Piercy Committee

Hunterian Society

The annual dinner, commemorating the 232nd anniversary of John Hunter's birth, was held in London on Feb 11

The toast of the Society was proposed by Sir Cyril Hinshelwood, president of the Royal Society, who said he was proud that Hunter had been a fellow of the Royal Society, for, although he would have been unorthodox in any age, the key to his greatness lay in his ability to see problems in their largest possible context and in terms of basic principles In his reply, Mr Alec Badenoch, the president, welcomed the guests, thanked the officers of his society, and reviewed the year's activities which had been popular rather than scientific, for, like Hunter, the society was unconventional

Dr Kenneth Robson, proposing The Lord Mayor and Corporation, spoke proudly of the society's link with the City and its privilege of using the Mansion House for the annual oration The Lord Mayor, Sir Edmund Stockdale, responded

Dr Clement Chesterman proposed The Guests and Kindred Societies In thanking the society on behalf of the " non-Hunterians " Lord Radcliffe said he was delighted to feel that he had been invited " as a person and not as a report " He went on to recall that Hunter had been one of the first expert medical witnesses to appear in a murder trial, when he had been criticised by the judge for being unable to answer " yes " or " no ", but, Lord Radcliffe added, this was a very bad judge

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Dr D A Pond will give a lecture for general practitioners at University College Hospital, London, S W 1, on Sunday, March 6, at 10 15 A M He will speak on new stimulants and tranquillisers in psychiatry

Births, Marriages, and Deaths

DEATH

TAYLOR —On Feb 15, Dr James Maberley Taylor of 17, Kent Terrace, London, N W 1

Appointments

BLACKSTONE, J W, M B W'srand house-surgeon, The Hospital for Sick Children, Great Ormond Street, London

CROSLAND MARGARET M, M B Manc, M C S P assistant M O, North East Cheshire

FULLER, ANGELA D, M B Cantab, D C H assistant M O, Middlesex (area 8)

GODDARD PEARL, M B Durh, D P M assistant psychiatrist (S H M O) St James Hospital, Portsmouth

HOWIE, G F A, M B Edin, M R C P E, D M R D consultant radiologist, Dundee teaching hospitals

MACGREGOR, D McC, M B Glasg, D P M consultant psychiatrist and deputy physician superintendent, Stratheden Hospital, near Cupar, Fife

STANFIELD J P M D Lpool M R C P, D C H senior medical registrar The Hospital for Sick Children Great Ormond Street London

STOKOE, N L, M B Edin F R C S E, D O consultant ophthalmologist Fife hospitals and clinics, Bangour Hospital, and Royal Infirmary Edinburgh

The Lancet · Saturday 27 February 1960

PLACENTA PRÆVIA*

C H G Macafee
M.B Belf, F.R.C S, F.R.C S I, F.R.C.O G
PROFESSOR OF MIDWIFERY AND GYNÆCOLOGY IN
THE QUEEN'S UNIVERSITY OF BELFAST

PLACENTA prævia has long been recognised as one of ie most dangerous complications of pregnancy Just ver a hundred years ago, the maternal mortality from his cause was 30% and the fœtal mortality 60% By 939, the maternal mortality had dropped to 5%, but the etal loss was little changed at 54% In 1945–50 the nodern views on the treatment were widely described, nd in the middle '50s the maternal mortality again fell ppreciably In some centres the perinatal fœtal mortality as now been reduced to around 10%

One reason for this improvement is that the attitude of oth doctors and midwives towards antepartum hæmorrhage has altered. They no longer look upon it as a urgical emergency which must be dealt with immediately n the patient's own home Hence in the vast majority f cases the patient is transferred to hospital without any ttempt to confirm the diagnosis of placenta prævia by aginal examination. This fact is evident from the Oxford and Belfast series in table I, which are shown in contrast to an Indian series (Qureshi 1953) where 80% of the deaths were in women who had been examined before admission.

TABLE I—THREE SERIES COMPARED

Series	No of cases	Maternal mortality	Perinatal mortality	Cæsarean section	No of examinations
R.M.H. 1946–53	200		11·9%	76%	2
Oxford 1948–59	217		9 7%	66%	
Qureshi 193–5	200	30 (*15%*)	67%	16%	24

R.M.H =Royal Maternity Hospital, Belfast.

Nevertheless, avoidable deaths are still occurring The report on confidential inquiries into maternal deaths in England and Wales 1952–54 shows that even within recent years the profession in England and Wales has not fully appreciated the essentials of treatment. During those three years 29 women died as the result of placenta prævia, and avoidable factors were considered to be present in 55% of these

> "There were often several avoidable factors in one case, a common combination being failure to anticipate trouble, in that anæmia was left untreated, warning hæmorrhage ignored or women of high parity booked for home confinement, then when hæmorrhage occurred, sometimes in a patient already unlikely to withstand it, the action was hesitant or plainly ill considered."

Today there should be no hesitation about transferring any case of antepartum hæmorrhage to hospital There are few exceptions to this rule, and I shall deal with them later

It should surely be obvious that a premature vaginal examination may precipitate a hæmorrhage. Such a hæmorrhage may necessitate immediate treatment, irrespective of the duration of the pregnancy This means an additional risk to both mother and baby

The next improvement has been the more general adoption of expectant treatment. We have long since got over Jaggard's dictum that "there is no expectant plan of treatment for placenta prævia"

Duration of Pregnancy

When a patient is admitted with antepartum hæmorrhage, the duration of pregnancy must be taken into account.

1 If the pregnancy has reached 37–40 weeks, delay in treatment is unwarranted. Having typed the patient's blood and determined the hæmoglobin level, one should not fail to make a diagnosis of the cause of the hæmorrhage. Examination of the abdomen will go a long way towards confirming or disproving the diagnosis of placenta prævia. If the presenting part is high, the fœtal heart (even after a moderate hæmorrhage) is undisturbed, and the uterus is not tender, the patient probably has a major degree of placenta prævia. If the presenting part is easily felt above the symphysis pubis and tends to overlap it, the placenta is posterior, while if the head is not easily felt unless the examining fingers approach it from either side, the placenta is in front.

The final answer can be given by a vaginal examination, but this should be done only with the patient on the operating-table. Such examinations have been criticised, but unless the position of the placenta is accurately determined many unnecessary cæsarean sections will be performed.

If the first episode of bleeding has been at 30–34 weeks, expectant treatment plays an important part The object should be to avoid any active treatment until the patient has reached 37–38 weeks, but whether this can be achieved depends on her behaviour from day to day The attendant's hands may be forced by the recurrence or persistence of bleeding of such degree that delay in treatment would jeopardise life Though spontaneous catastrophic hæmorrhage is extremely rare—so rare that Dr Herman Johnson in the U S.A. felt confident enough to challenge anyone to produce a case—persistent or repeated small hæmorrhages may result in serious maternal anæmia.

During expectant treatment, measures should be taken to improve the patient's general condition, and blood-transfusion may often be required to correct anæmia quickly

Evidence of the value of expectant treatment is given in table II, which analyses series of cases collected from hospital reports

To show that the 75 cases in Belfast were not loaded favourably with mature babies I should point out that 25 of the 75 patients had their first hæmorrhage before the 30th week. In these 25 the shortest time between admission and treatment was twelve days and all were delivered of live babies Unfortunately, 3 of these died in the neonatal period, but even in this unfavourable group the fœtal mortality was only 12%

TABLE II—MORTALITY IN RELATION TO EXPECTANT TREATMENT

Series	No receiving expectant treatment	Fœtal mortality	Maternal mortality
1553	257 (*16 5%*)	14·7%	0 79%
1353	187 (*13 8%*)	20·8%	1·07%
200 (R.M.H.)	75 (*35%*)	8·5%	

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* From a lecture given at Queen Charlotte s Hospital, London, on Sept 25, 1959

X-ray Diagnosis

It is in cases of antepartum hæmorrhage at 30–37 weeks that X-ray diagnosis may be of assistance. At this stage accurate clinical diagnosis can be difficult unless the fœtal head is deeply engaged, although a thin placenta prævia may not prevent engagement. With modern radiological techniques the placenta can be located in a fairly high proportion of cases, but one must remember that with placenta diffusa or membranacea, or a placenta on one side of the lower uterine segment, the X-ray appearances can be frankly misleading. If in doubt, the case must be treated as one of placenta prævia until 37 or 38 weeks.

In the discussion on placentography at the Royal Society of Medicine in January, 1959, very diverse views were expressed. Some teachers would use placentography in all cases of antepartum hæmorrhage, or a high free head, whereas others regard it as quite unnecessary or even "dangerous nonsense." Personally I am relieved to find that even some of its earlier advocates have now discarded this type of examination. In my hospital placentography has not been done for some years, and X-ray pelvimetry is almost a thing of the past. In the course of the discussion Dr. Blair Hartley said:

> "I do not accept that adequate placentography can be carried out using only a single lateral view with the patient lying down (as has been claimed). Even with four films, carefully planned, really adequate opinion is, not infrequently, very difficult to offer, even in expert hands." (Hartley 1959.)

Coming from a radiologist, and an advocate of placentography, I would regard this as complete condemnation of this method of examination. As an obstetrician Mr. John Stallworthy said:

> "The idealistic goal which had been set in the treatment of placenta prævia over ten years ago, namely, that there should be no maternal deaths and an uncorrected fœtal wastage of 10 per cent or less, had been achieved, but in doing so it had been found that the radiological diagnosis was seldom necessary."

Four possible causes of the bleeding have to be considered:

1. Placenta prævia.
2. Separation of a normally situated placenta.
3. Hæmorrhage from a circumvallate placenta.
4. Toxic accidental hæmorrhage in a patient with a placenta prævia.

The other local causes of antepartum hæmorrhage—e.g., cervical polyp and carcinoma of cervix—should be excluded by passing a vaginal speculum and inspecting the cervix.

Percival and Murray (1955) maintained that soft-tissue placentography could reduce the use of valuable antenatal beds for cases of antepartum hæmorrhage. They wrote: "In non-toxic accidental haemorrhage, once placenta prævia has been excluded and bleeding has ceased, the patient can be safely sent home." I am afraid I cannot agree with this, for even non-toxic accidental hæmorrhage seems to carry a fœtal mortality higher than that of placenta prævia treated by modern methods. If I am right, the differentiation between non-toxic accidental hæmorrhage and hæmorrhage from placenta prævia is of little practical value at this period of gestation, since the patient should in any case be retained in hospital for investigation and observation.

The circumvallate placenta is often associated with small recurrent antepartum hæmorrhages, but several other features help in the diagnosis. The uterus seems smaller than the period of amenorrhœa would suggest, the baby is small, and the presenting part is usually well engaged. In addition, placentography may demonstrate the placenta in the upper uterine segment, and there is no evidence of toxæmia.

Association of a placenta prævia with a toxic accidental hæmorrhage does raise difficulties in diagnosis and treatment, but it is a possibility that must be considered where a patient with an undoubted placenta prævia has gross albuminuria and perhaps hypertension.

TABLE III—MORTALITY IN RELATION TO CÆSAREAN SECTION

Series	—	Perinatal mortality	Maternal mortality	Cæsarean section
R.M.H.	1937–45	22%	0·52%	41·3%
	1946–53	11·9%		76%
	1954–58	12·5%	1·5%	67·7%
Oxford	Last 217 cases	9·7%		66%
Qureshi	1934–39	71·3%	21·9%	8·9%
	1940–45	60·2%	5·8%	26·7%

Treatment

The patient who has had a long spell of expectant treatment has the scales weighted heavily in favour of cæsarean section as the method of treatment most likely to result in a living child. Table III, setting out results in several series, suggests that both maternal and fœtal mortality are lower where the operation is performed often.

In Qureshi's Indian series one would have expected a much greater fall in the fœtal mortality when cæsarean section increased, but he was working in conditions quite different from those of the United Kingdom today. Broadly speaking, the higher the cæsarean-section rate the lower should be the perinatal mortality, provided the patients are being carefully selected and properly treated before operation. Qureshi's series demonstrates the importance of this proviso, for he is forced to deal with patients who have been examined vaginally before admission (table I) or have been admitted in irreversible shock.

Lower-segment cæsarean section is the operation now most frequently performed, but I do not think that the abdomen should be opened with the preconceived idea of invariably carrying out this type of operation. Circumstances may make it difficult—for example:

1. *A poorly developed lower uterine segment.*—This is unusual, but it is very obvious when the abdomen is opened, because all the available lower segment is behind the symphysis pubis, making its exposure difficult. If one persists in trying to perform the lower-segment operation, the lives of both mother and child may be jeopardised. It takes a relatively long time, and almost inevitably the large vessels on either side will be cut or torn.

2. *Adhesions obliterating the operation site.*—This state of affairs is, of course, unlikely unless the patient has had a previous cæsarean section or a low anterior myomectomy.

3. *Marked vascularity of the lower uterine segment.*—This is commonly regarded as an indication for the classical operation, but it need not rule out the segment procedure if the lower uterine segment is well developed and the operator is experienced. Vascularity of the lower segment is common especially when the placenta is situated anteriorly, and it is an indication for rapid enlargement of the incision in the lower segment, with rapid but careful extraction of the baby.

There are few occasions on which the classical operation has to be performed, and from the point of view of future pregnancies this is fortunate. On the other hand, one must be ready to perform it whenever necessary.

Cæsarean section is desirable in most cases where there is a major degree of placenta prævia, even when the period of gestation is still under 36 weeks With modern pædiatric care a very large proportion of premature babies can be saved

The situation of the umbilical cord in relation to the internal os can be of vital importance Very often the cord is situated excentrically, and usually this does not matter much, because its excentric insertion is far away from the internal os But where the insertion is just inside the internal os, cæsarean section may be the only means of delivering a live child The importance of this is evident from the fact that in the first Belfast series (table III) at least 9 of the 33 deaths in babies were directly due to malposition of the cord

The relation of the cord to the anterior part of the lower uterine segment is also important at a cæsarean section If it is anterior there is a risk that the cord, or one of the big vessels close to it, may be divided, resulting in the delivery of an anæmic baby An incision into placental tissue is another indication for rapid delivery of the fœtus

While cæsarean section has undoubtedly improved the results for both mother and baby, it can have complications necessitating quick decisions and perhaps radical surgery

Occasionally there is persistent, apparently uncontrollable, hæmorrhage from the lower uterine segment. This may follow the removal of the placenta while the abdomen is still open, and a decision must be made as to whether a hysterectomy is necessary or not In a multigravida it may be the safest method of treatment, but in a primigravida it will almost certainly be unnecessary Replacement of blood-loss, and packing the upper and lower segments with gauze (which later can be removed per vaginam), may be all that is required When bleeding follows closure of the abdomen, it can usually be controlled by the same method, but the intrauterine pack must fill the whole uterine cavity, and ergometrine must be given to make the uterus contract on it

Placenta accreta is a complication that may have to be faced as soon as the uterus is opened, especially if the placenta is attached to the anterior part of the lower uterine segment On incising the placenta one sees no line of demarcation between it and the uterine wall, and at this stage there is actually less bleeding than if the implantation was normal This complication, in association with placenta prævia, is rare, but " in most reported cases of placenta accreta there is a high incidence of implantation of part or all of the placenta in the lower segment " (Millar 1959)

The abnormal adhesion may involve the whole placenta or only the portion attached to the lower segment Where the whole placenta is involved, or where the condition is one of percreta, hysterectomy has to be performed Attempts to separate the abnormally adherent placenta are associated with a high mortality from shock and hæmorrhage

Apparently, a small localised area of placenta accreta can be left with safety, and I have done this on one occasion without untoward result Kaltreider (1945) quotes 7 cases where the whole placenta was left in situ and all recovered, and Schumann (1940) described 4 cases successfully treated, in the same way, in 2 of which a normal pregnancy followed Millar (1959) has left the accreta portion in the lower segment in a primigravida of 19 without subsequent complications

In 1954–58 two women died in the Royal Maternity Hospital, Belfast, from shock and hæmorrhage after cæsarean section

One was a 9-gravida with a placenta accreta too much time was spent in trying to remove it manually, and hysterectomy was undertaken too late The other, a 3-gravida who had had two previous cæsarean sections, was admitted at 26 weeks with a threatened miscarriage At 34 weeks bleeding was profuse and a classical cæsarean section was performed This was uneventful, but two and a half hours later she collapsed with uterine bleeding and died.

In the first case a hysterectomy at an earlier stage would almost certainly have saved the patient In the second case the collapse may have been due to unrecognised postoperative uterine relaxation and intra-uterine bleeding It emphasises the importance of careful postoperative supervision

Rupture of the Membranes

Though 60–70% of cases of placenta prævia are now delivered by cæsarean section, artificial rupture of the membranes has still an important place in the treatment of the less severe varieties The fact that such a large proportion of cases is delivered by cæsarean section suggests that the lesser degrees of placenta prævia are uncommon But in point of fact many cases of the first degree escape diagnosis because they never have any antepartum hæmorrhage, or nothing more than an excessive show during labour On the other hand, some minor degrees can bleed quite profusely, and many unnecessary sections will be performed if one makes the mistake of doing cæsarean sections without preliminary vaginal examination

Where the presenting part can be felt through all the fornices, and the placental edge is reached only after introducing the finger into the lower uterine segment, artificial rupture of the membranes will almost certainly suffice If the placenta is lying in the second-degree position anteriorly, rupture of the membranes is again likely to be successful If the placenta is lying posteriorly and the presenting part can be pushed into the pelvic brim without disturbing the fœtal heart, rupture of the membranes is probably the correct treatment in a multipara If, on the other hand, pressing the fœtal head into the pelvic brim disturbs the fœtal heart, the umbilical cord is almost certainly situated excentrically in close proximity to the lower edge of a second-degree placenta prævia and near the internal os In such a case rupture of the membranes may result in prolapse of the cord or compression of the cord by the fœtal head, which forces one to perform a rapid cæsarean section in unfavourable circumstances or perhaps be faced with an intrauterine death before the operation can be performed In addition, the posteriorly situated placenta is more liable to prevent engagement of the head, and persistent bleeding may result from the failure of the fœtal head to compress the separated placenta

Version

The virtual abandonment of bipolar version has been another important factor in reducing the perinatal mortality, and also, to some extent, the maternal mortality

This operation has a fœtal mortality of between 60–80% and is now reserved for a few selected cases It has a definite place where the baby is very immature or already dead, and it is occasionally indicated in the multipara who has a good obstetric history and is in labour with hæmorrhage of such a degree that it must be controlled before any further steps can be taken Here the baby may be alive, and may even be born alive if the version is carefully and gently performed, and the placenta prævia is of a moderate or minor degree

It has been suggested that in these cases a preliminary external version facilitates extraction of the foot and reduces the amount of internal manipulation required This is true provided the legs are not extended If they are, it will actually increase the internal manipulation and make the extraction of the foot more difficult

Apart from the type of case I have mentioned, podalic version now has a very small place in the treatment of placenta prævia in the United Kingdom and most of the Western world

Criticisms

When I visited the Rhodesias and South Africa as Sims Black professor, I was criticised for my attitude towards the treatment of placenta prævia, and especially for what I said on expectant treatment and cæsarean section I was told that I had oversimplified the subject and that some of my teaching was not applicable to the African patient—indeed was unwise In view of what I saw and heard on my visit I believe that some of these criticisms are sound

I still maintain that the modern treatment of placenta prævia has justified itself, but it depends on hospital and medical facilities which many communities in many countries do not yet possess I have not visited India, but Dr Qureshi's paper criticises expectant treatment in a way that demands attention, and expresses opinions which would be valid in South Africa and possibly some Far Eastern countries He says

> "The present day emphasis on expectant treatment by several authorities notably Macafee (1945), Williamson and Greeley (1945) Johnson (1945) and others and the remarkable reduction in the fœtal mortality reported by them, is likely to excite the enthusiasm of many obstetricians for this method of treatment But every obstetrician must be alive to the environment in which he is practising and the type of patients he is to treat
>
> "There are very few hospitals in this sub-continent which are well equipped, well staffed and highly organised. Even if there were a profusion of well-organised institutions, the type of patients we get should not be lost sight of From my experience of six years at the Lady Willingdon Hospital, Lahore, and Victoria Jubilee Hospital, Amritsar, with obstetric patients, I can state without fear of contradiction that our patients are extremely gullible and lend themselves easily to vaginal examination by dais Even they make their own vaginal examinations One of the patients in the present series undergoing expectant treatment in hospital did her own vaginal examination!
>
> "Many of them when admitted to hospital are very co-operative, and ready to accept all conditions for treatment But later on they get weary All of a sudden, as if possessed by a demon, they leave the hospital at their own risk They become completely impervious to otherwise convincing reasoning No amount of persuasion or vivid presentation of frightful consequences can deviate them from their irrevocable decision to leave the hospital This applies to all types of cases, whatever their status The two cases in which death occurred on readmission were private cases!
>
> "In view of these facts, I am of opinion that very serious thought must be given to the prevalent conditions before deciding upon expectant treatment of placenta prævia. At present it should be exception rather than the rule When an adequate number of well organised institutions comes into being and the patients are delivered from the clutches of ignorant but all powerful dais and they become, through proper education, more susceptible to rational suggestion for treatment and more consistent in their behaviour, then and then alone can the expectant treatment be instituted on a more extensive scale, with perfect safety to the mother"

In South Africa the frequent use of cæsarean section was also criticised not only because facilities for the operation may be inadequate but also because of the risk of ruptured uterus at subsequent confinement and because of the very high infant mortality

It was pointed out to me that, before leaving a scar in the uterus of a Bantu patient, one must consider her possible subsequent history Her next baby may be born in the kraal with no expert medical or nursing care and the uterus may rupture and the patient die In Rhodesia I myself had to operate on a woman who had ruptured a cæsarean-section scar in the Bush two days before admission to hospital

The infant mortality is relevant because operation on the mother in order to save the child may seem less imperative when the child's prospects of later survival are so much less than they are here In Port Elizabeth in South Africa the annual report of the Medical Officer of Health shows that in 1955 the mortality per 1000 in the first year of life was

European	35·87
Eurafrican	135·6
Asiatic	32·26
Bantu (city only)	356·00
All non-Europeans	218·69

From an ethical standpoint this argument is difficult to defend, but with perhaps one child in three dying before the age of 12 months, more weight attaches to the risk of the mother dying of ruptured uterus at a subsequent confinement

Qureshi feels that in the environment in which he has to work some of the older methods of treatment should be retained he would advocate the use of podalic version almost as frequently as it was used in this country before 1945, and, despite Prof F J Browne's condemnation of them some years ago, he regards Willett's forceps as valuable Indeed he uses them even in relatively major degrees of placenta prævia, whether the presentation is a vertex or breech

Though I rarely use Willett's forceps I believe they occasionally have a place where the placenta is anterior and where some bleeding persists after artificial rupture of the membranes Gentle traction not only controls the bleeding but stimulates uterine contractions, with the result that the forceps have only to be applied for a short time But I would not agree with their use in a breech If the baby is alive, extraction of a foot is the safer and more rational method of treatment if it is dead, version is safer and more effective

It is important for us in the United Kingdom to remember that our situation is exceptional in that hospitals, blood-transfusion, and experienced medical and nursing care are never very far from any patient Elsewhere the distances are often great, the patient is more often ignorant, and the doctors are more likely to lack specialised experience Only by taking this into account can we appreciate the importance of environmental factors in deciding how to treat a case of placenta prævia

I would like to thank Miss Roma Chamberlain, of the Ministry of Health, London, for supplying me with data

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THE CARPAL-TUNNEL SYNDROME IN PREGNANCY

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PAIN and tingling in the arms and hands during pregnancy are fairly common symptoms, but relatively little attention has been drawn to them as they often do not arise until the last 3 months of pregnancy, and they tend to improve after delivery In a few cases, however, the patient is in constant pain during the day and is unable to sleep at night

This series comprises fourteen patients, all of whom were seen during pregnancy, and all but two also after delivery Seven had compression of the median nerve only The other seven had signs of median-nerve compression combined with signs of compression of one or more cervical nerve-roots, suggesting a common pathogenesis One other patient with signs of bilateral median-nerve compression, seen when she was 74, gave a history of numbness and tingling in her hands for 38 years, the symptoms having started when she was 6 months pregnant with her second child

Acroparæsthesiæ in pregnancy have been described by Walshe (1945), Garland et al (1957), and Heathfield (1957), amongst others Various theories have been put forward to explain compression of the median nerve during pregnancy Guly (1959) and others believe that salt and water retention is the most important mechanism. Hence diuretics have been given by mouth in treatment with some success (McCallum 1959, Wood 1959) Injection of hydrocortisone 0 5–1 0 ml into the carpal tunnel may also give dramatic relief in a high proportion of cases, including those associated with pregnancy (Philip 1959)

Ætiology

The main ætiological factors in compression of the median nerve in the carpal tunnel during pregnancy are trauma, a rapid or unusually great increase in weight, and, perhaps, changes in fluid content or tension of the ligaments But relaxation of the carpal ligament can only be important if it causes the relation of the structures in the carpal tunnel to be changed Preexisting cervical spondylosis seems to play a part in the syndrome, possibly by partially damaging nerves so that further pressure causes symptoms

Trauma

It has been recognised for some time that trauma may produce the symptoms of compression of the median nerve in the carpal tunnel (Brain, Wright, and Wilkinson 1947), and any occupation involving forcible dorsiflexion of the wrist may precipitate them Many household jobs come under this heading Three patients started to get symptoms when they gave up a sedentary office job and started doing housework, in one shortly after cleaning a large carpet, and in another after interior decorating In another the symptoms appeared very early in pregnancy (the 13th week), 5 weeks after she had taken a job which involved lifting heavy laundry baskets Seven patients gave a history of trauma just before the onset of their symptoms

Weight Increase

Chesley (1944) estimated that the average woman gains 24 lb during pregnancy—that is an average increase of 24% of the prepregnancy weight Two-thirds of all pregnant women gain 13–35 lb , one-sixth more than 35 lb , and one-sixth less than 13 lb The average gain in weight during the first 3 months of pregnancy is not more than 3 lb , but during the 2nd and 3rd trimesters the gain averages 1 lb per week until shortly before labour, when up to 3 lb may be quickly lost. The loss continues postpartum, but afterwards there is a net gain of 6 lb Five patients in this series gained 30 lb or more in weight during their pregnancy One patient gained 60 lb during her second pregnancy During her first pregnancy the gain in weight had not been excessive, and she did not have symptoms in her hands In the second pregnancy paræsthesiæ came on early, affecting her right hand in the 19th week, by which time she had already gained 27 lb Paræsthesiæ did not affect her left hand until the 33rd week. In four other patients there was marked increase in weight, in three paræsthesiæ developed within 4 weeks of a rapid gain in weight, the average increase being 10 lb in 4 weeks

Relaxin

Hisaw (1926) postulated a hormone, relaxin, which had a specific effect on the relaxation of the symphysis pubis in the guineapig Sands (1958) showed that this hormone modifies the pelvic joints in pregnancy, and Sands and Stone (1959) showed that relaxin is a protein or polypeptide soluble in water and highly stable It has been demonstrated in the blood of pregnant women, increasing in concentration until the 38th week, and disappearing rapidly within 24 hours of parturition Boucek (1955), using a sponge-biopsy technique, studied the histochemical characteristics of connective tissue in different age-groups He showed that when the host was treated with relaxin the collagen-fibres became finer and more widely separated, the ground substance was depolymerised, the mast-cells increased in number, and more fluid was imbibed

The increase in fluid intake may be important in producing the symptoms of median-nerve compression in pregnancy, as it would increase the volume of the contents of the carpal tunnel Since all ligaments tend to relax during pregnancy, it is reasonable to suppose that those of the carpal tunnel are involved, and that alteration of the stresses and strains at the wrist may play some part in the production of symptoms

Other Factors

Posture during sleep may be important Four patients were more comfortable sleeping on their backs during the last few weeks of pregnancy, and five found that the paræsthesiæ were worse if they slept on the affected side During the day fluid tends to accumulate in the legs, but this tendency is reversed at night when the patient lies flat This redistribution of fluid may play some part as the symptoms were always worse at night or on waking, even when they persisted through the day Because radiographic changes were not very conspicuous in the cervical spine, the factors discussed above may have contributed to the radicular symptoms when these were present.

Clinical Features

Symptomatology

All the patients in this series complained of numbnesss, tingling, or pain in the fingers of one or both hands

In the majority the numbness was in the thumb, index, and middle fingers, or in the index and middle fingers In one the index, middle, and ring fingers were affected, and in another the ring and little fingers were worse although all the fingers were affected. Twelve of the patients were right-handed, and in all but two the symptoms started in the dominant hand In nine one hand only was affected, and in the other five both hands were involved Where both hands were involved the dominant hand was affected earlier in three and the symptoms came on in the opposite hand 1, 9, and 14 weeks later In two cases both hands were involved simultaneously

Pain in the neck and shoulder was experienced in two cases, and pain in the wrist and forearm in five

Seven patients had objective swelling or feelings of tenseness of the hands, in one swelling was so severe that she had to have her wedding ring cut off No patient in this series had toxæmia of pregnancy Backache was not common, occurring in only four patients

Of the seven patients with symptoms due to a combination of median-nerve and cervical-root pressure four showed flattening and one showed exaggeration of the normal cervical curve The seven patients with median-nerve compression only were slightly younger than those with both nerve and root compression (26 7 years compared with 29 7 years) In five cases the symptoms appeared during the first pregnancy

None of the patients had had symptoms for long The average time for the whole group was 10 1 weeks, for those with median-nerve compression only it was 7 9 weeks, and for the mixed group 12 4 weeks The symptoms usually improved after delivery, in four patients they disappeared within 48 hours but in most residual symptoms persisted for 1–4 weeks One patient improved while she was resting in bed for 2 weeks before delivery In two the symptoms persisted One of these required decompression of the median nerve 10 months after delivery, this was the only patient needing operation The other patient who did not improve continued to have pain in her arms, and radiographs 9 months later showed the characteristic changes of cervical spondylosis

Physical Signs

Impairment of awareness of pinprick or cotton-wool in the distribution of the median nerve was the most common sign, being found in eleven of the fourteen patients Only three showed wasting and weakness of the thenar muscles Reflex changes were found in five patients who had compression of the median nerve and of one or more cervical nerve-roots, one or both triceps jerks were diminished in four, and the biceps jerks in one Movement of the cervical spine was limited in three patients, and in three there was drooping of one shoulder One patient who was heavily built had a short thick neck with a marked upper dorsal kyphosis

Radiological Changes

The cervical spine was X-rayed in twelve cases Eight showed slight loss of the normal curve, four had diminution of one or more disc spaces, and two showed narrowing of the intervertebral foramina Since none of the patients gave a history of injury to their wrists these were not X-rayed routinely

Treatment

Because the symptoms were usually worse at night or in the early morning sleeplessness was one of the main complaints Hence a sedative such as amylobarbitone sodium was given, together with an analgesic Patients were advised not to lie on the affected arm, as this tended to make the symptoms worse In most cases this was the only treatment required

Splinting was sometimes helpful, being used for three patients, one improved a good deal, another improved slightly, and the third was unchanged A light splint, applied to the dorsal surface of the wrist, was bandaged around the palm and forearm, the wrist being kept in the neutral or slightly flexed position The palmar surface of the wrist should never be splinted as this tends to increase the pressure on the median nerve, making the symptoms worse

During pregnancy the symptoms are rarely sufficiently severe to require immediate operation, and, as they tend to improve spontaneously during the puerperium, operation should be delayed until after delivery Symptoms persisted after delivery in only one patient in this series, she was operated on several months later, with relief

Where the symptoms were due to compression of the median nerve and cervical nerve-roots sedation was combined with active exercises for the neck and shoulders Seven patients were so treated, with some improvement in four

Summary

In fourteen patients symptoms due to compression of the median nerve in the carpal tunnel appeared during pregnancy Seven also had symptoms of cervical radicular lesions

Trauma may precipitate the median-nerve compression in some cases, but the metabolic changes, and especially fluid retention, associated with pregnancy appear to be the main causal factor

The immediate treatment is symptomatic Since most patients recover spontaneously after delivery, operation should be deferred and is then rarely necessary

My thanks are due to Sir Russell Brain for his help and advice, and to Miss M H Calverley, Miss W F Lewington, and Miss J A M Moore for referring patients to me

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HYDROCORTISONE AND THE CARPAL-TUNNEL SYNDROME

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THE commonest cause of acroparæsthesiæ limited to the distribution of the median nerve in the hand is now widely accepted as compression of the median nerve in the carpal tunnel Since the initial description by Brain et al (1947) of symptomatic relief by simple retinacular section many reviews of the pathogenesis of the syndrome and its surgical treatment have appeared (Wolfman 1944, Nissen 1952, Kremer et al 1953, Grokoest and Demartini 1954, Garland et al 1957, Heathfield 1957, Phalen and Kendrick 1957, Vainio 1957, Dick and Zadik 1958, Wiley 1959)

Acroparæsthesiæ in the median-nerve distribution may occasionally arise in the course of systemic disease, such as rheumatoid arthritis, myelomatosis, or amyloidosis (Grokoest and Demartini 1954, Keith 1957) The syndrome not infrequently follows fractures at the wrist, and it may be associated with ganglia of tendon sheaths or with capsular thickening of rheumatoid disease of the wrist-joint itself But most cases arise in middle-aged women without general disease or local lesion at the wrist

If compression of the median nerve is secondary to non-specific thickening of the tendon sheaths entering the carpal tunnel, then the nocturnal exacerbations which are so constant a feature may well be due to the increase in bulk of this enclosed tissue by the generalised vaso-

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INITIAL FINDINGS AND RESULTS IN TWENTY CASES OF CARPAL-TUNNEL SYNDROME TREATED BY HYDROCORTISONE INJECTIONS

Case no	Sex	Age (yr)	Side affected	Duration of symptoms (mos)	Symptoms						Associated disorder	Results of treatment*									
					Pain	Numbness	Tingling	Arm pain	Weakness of abductor pollicis brevis	Sensory loss		Weekly assessment			6-weekly follow-up	Intermediate follow-up (mos)	Intermediate result	Final follow-up (mos)	Final result	Time of relapse (mos)	Operation
												1	2	3							
1	F	41	R	3	+	+	+	+				+	++	c	c	7	c	15	c		
2	F	48	L	1½	+	+	+	+		+	Goitre	+	c	c	c	6	c		?		?
3	F	45	R	5	+	+	+					+	c	c	c	4	r	13	—		
4	F	65	L	8	+	+	+			+	Diabetes	—	+	++	c	5	c	14	c		
5	F	40	L	6	+	+	+				Diabetes	c	c	c	c	5	c	14	c		
			R	6	+	+	+					c	c	c	c	5	c	14	c		
6	F	44	R	6			+				Epilepsy	+	++	c	c	4	c	12	r	4	
7	F	52	L	18		+	+				Epilepsy	+	c	c	c	5	c	13	r	6	+
			R			+	+					—	+	c	c	5	c	13	r	6	+
8	F	51	R	6	+	+	+	+			Depression	—	+	c	c	4	c	12	r	5	+
9	F	51	R	36		+	+	+		+		+	++	++	c	4	c	12	r	6	+
10	F	51	L	6		+	+					+	+	c	c	6	c	15	r	11	
11	F	25	L	1½		+	+				Arthritis	c	c	c	c	8	c	16	r	14	
			R	2		+	+					c	c	c	c	8	c	16	r	14	
12	M	25	L	3	+	+	+	+			Diabetes	++	c	c	c	6	c	15	r	9	
			R	3	+	+	+	+				++	c	c	c	6	c	15	r	9	
13	F	47	R	12			+				Epilepsy	+	++	++	c	3	c	14	r	6	
14	F	41	R	3	+	+	+	+			Anxiety state	—	—	—	—	3	—				+
15	F	43	R	9	+						Diabetes	—	—	—	—	4	—				+
16	M	62	R	2	+	+	+	+	+	+	Cardiac infarction	+	+	+	+	3	+	11	r	8	
17	F	52	R	24	+	+	+					+	++	++	++	6	++	16	r	15	
18	F	45	R	3	+	+	+			+	Depression	—	—	++	c	4	c	12	c		
19	F	64	L	6	+	+	+					—	—	+	++	5	++	12	r	6	
			R	18	+	+	+		+	+		—	—	++	++	5	c	12	c		+
20	F	54	R	9	+	+	+		+	+	Diabetes	—	—	++	c	5	r	14	—		

* + = some improvement, ++ = great improvement, — = no improvement, c = symptom-free, r = recurrence of symptoms

dilatation of deep sleep The constant trauma provoked by flexion-extension movements at the wrists has been invoked as the cause of the more persistent symptoms on which these characteristic exacerbations are superimposed

Non-specific inflammatory swelling of soft tissues responds well to the injection of hydrocortisone Hence, drawing a loose analogy between the tenosynovial swelling of the flexor tendons in and above the carpal tunnel and the synovial thickening of the rheumatoid joint, I decided to observe the effect of hydrocortisone instilled into the carpal tunnels of a series of patients with median-nerve acroparæsthesiæ, as suggested by Phalen and Kendrick (1957)

Investigation

The Patients

Twenty patients were referred from the outpatient department of a general hospital for treatment (see table)

All fulfilled the criteria of pain or paræsthesiæ in the median-nerve distribution of the hand for more than 6 weeks, aggravated by exercise at the wrist, and with nocturnal exacerbations Some had unrelated systemic disorders as shown in the table Sensation (light touch, pinprick, and two-point discrimination) was examined in all cases, and the muscles supplied by the median nerve were tested for power, particular attention being paid to the strength of the abductor pollicis brevis Radiographs of the cervical spine were taken in each case to exclude "cervical rib"

Technique

Hydrocortisone tertiary butyl acetate (Merck) 1 ml (25 mg) was injected into the volar aspect of the wrist at the junction of the medial edge of the palmaris-longus tendon and the proximal border of the retinaculum Three injections were given into each wrist at weekly intervals, and the symptoms and signs were reviewed each week thereafter

The skin was prepared with spirit and iodine A 'Star' 20 needle (1 5 cm long) was used, being introduced to maximum depth at an angle of 45° to the surface of the arm in its longitudinal axis (Injection of the wrists of cadavers with coloured solution confirms that the substance comes to lie deep in the tunnel, so that on movement it will circulate amongst the tendons below the retinaculum, coming into contact with the nerve itself on its deep aspect) Patients were encouraged to use the hand after injection and not to restrict their activity

Results

The progress of each case is shown in the table Of the twenty patients, one wrist only was affected in fifteen Of these, ten had become symptom-free 3 to 8 months after the third injection of hydrocortisone Of the other five patients in whom both wrists were involved, eight wrists became similarly symptom-free Three of the remaining seven wrists improved so much that the symptoms became tolerable and the patients did not wish to have further treatment In two others the symptoms recurred after a period of improvement, and the remaining patients who had in no way benefited by injection, were referred for operation

Thus twenty-five carpal tunnels were injected with complete relief of symptoms in twenty, partial relief in three, and no improvement in two Assessment after 12 months, however, showed a high relapse-rate in those who had initially improved, symptoms recurring in fourteen wrists Of the original twenty who obtained complete relief only six were symptom-free after 12–14 months, and five more needed surgical treatment

Discussion

Most patients who responded did so after the first injection Many experienced an exacerbation of symptoms during the 24 hours after injection, which was never prolonged. But in view of this the injection of more than 1 ml of fluid into an already tightly packed compartment is probably unwise Only seven cases showed objective signs of median-nerve damage—namely, clinically detectable sensory loss and thenar atrophy—and these signs had not improved at the time of intermediate follow-up (see table)

This investigation suggests that hydrocortisone injected into the carpal tunnel by the above technique will give temporary relief of acroparæsthesiæ in many cases without evidence of severe median-nerve damage, and more permanent relief in a few A larger group of patients is now being studied to discover whether nerve conduction-time is improved by the procedure, which provides a relatively painless and economical alternative to surgical treatment

Summary

Hydrocortisone was injected into twenty-five carpal tunnels of patients with median-nerve compression

The symptoms remitted completely in twenty cases, three derived some benefit, and two did not improve

This form of treatment, which is simple, relatively painless, and economical, may be preferable to operation in early cases without evidence of severe median-nerve damage, or with some contraindication to surgical treatment Unfortunately the relapse-rate is high

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A HITHERTO UNDESCRIBED PHENOMENON IN ABO HÆMOLYTIC DISEASE OF THE NEWBORN

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THE serological diagnosis of ABO hæmolytic disease of the newborn is sometimes very difficult The Coombs test is generally negative or very weakly positive, and the titre or nature of the maternal antibodies bears no clear-cut relationship to the severity of the baby's affection For early diagnosis many tests involving examination of the cord blood have been suggested, none is reliable, and close observation of all newborn children and measurement of indirect-reacting serum-bilirubin whenever early or deep jaundice exists, are the only sound guides to diagnosis and treatment (Tovey et al 1959)

The aim of the present paper is not to add a further test but to describe a phenomenon which until now does not seem to have been observed Erythrocytes suspended in an agglutinating serum sediment more quickly than those suspended in a compatible serum (Sander and Sander 1939, Stats 1950) We have shown that the hastening of the sedimentation is conditioned by, among other factors, the intensity of the agglutination, the packed-cell volume of the preparation, and the nature of the medium in which the agglutinated cells are suspended (Lewi 1954) We therefore decided to investigate the behaviour in this respect of erythrocytes from infants with hæmolytic disease Obviously, the erythrocyte-sedimentation rate (E S R) of whole cord blood cannot have any significance for this purpose, the E S R of cord blood is always very low (much lower than that of normal adult blood) owing to the composition of newborn's plasma (poor in α and β globulins and in fibrinogen) and to the high hæmatocrit level, whereas the tendency towards rouleaux-formation is the same in fœtal and in adult cells (Lewi 1955) Thus, for study of the action of antibody fixation on the red corpuscles of the baby, it is necessary to compare samples containing erythrocytes entirely free of plasma, suspended in a constant medium under a constant concentration

Material and Methods

Unclotted cord-blood samples were obtained on heparin (0 1 mg of pure heparin per ml of blood) The blood was centrifuged, the plasma removed, and the cells washed three times in neutral-phosphate-buffered isotonic saline solution. The red cells, as completely packed as possible, were mixed with polyvinyl-pyrrolidone (P V P) medium, and prepared as described later, in the proportion of 1 vol of packed cells to 3 vol of P V P medium The tubes were shaken gently and sedimentation was carried out in a Westergren tube (200 mm. high, 3 mm internal diameter) Readings were taken every 5 minutes The 10 min and 15 min readings are of the most interest

The P V P medium was made up by diluting 25% concentrated P V P (' Subtosan retard ', Specia) in normal isotonic saline The dilution was chosen in such manner that a 1 3 (v/v) suspension of fresh cord erythrocytes, washed and packed as above, of normal ABO-compatible full-term infants showed an average E S R of 5 mm in 10 minutes The final dilution of P V P giving such a result varied widely between different batches, and may range between 1% and 2 4% Once the dilution has been determined, the same batch may be used for several hundred tests

Many hæmatological and immunological tests were performed simultaneously on the cord-blood samples they will not be described here

Mother's blood for titration of incompatible anti-A or anti-B antibodies was obtained generally on the day of delivery, but sometimes 1 or 2 days afterwards Titration was made on A_1 or B adult red cells (1) in saline at room temperature and (2) in human AB serum at 37°C, hæmolysins, if present, were titrated in inactivated serum to which fresh human group-O serum known to contain no hæmolysins had been added

The newborn children were looked after by the hospital pædiatrician When necessary, hæmatological examinations and indirect-reacting bilirubin measurements in the baby's serum served as a guide for treatment, independently of our laboratory findings The policy was to perform an exchange-transfusion with group-O blood when the indirect bilirubin reached 20 mg per 100 ml , and a simple transfusion of packed cells when the red-cell count dropped below 3×10^6 per c mm Most of the children with deep jaundice, compatible or incompatible, received cortisone treatment (10–20 mg of Δ-cortisone by mouth daily for 3 or 4 days)

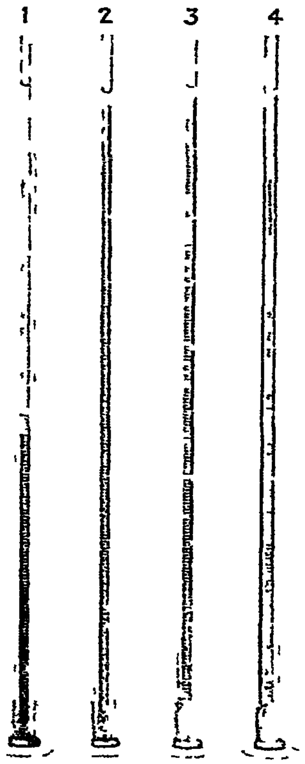
Results

Of 3924 cord-blood samples, 835 were incompatible in the ABO system with the mother's group (Children affected by Rh-hæmolytic disease, stillbirths, and children who died or left the clinic less than 3 days after birth are not counted) The distribution of incompatible children was as follows

Mother O, child A	416 cases
Mother O, child B	147 "
Mother A, child B or AB	146 "
Mother B, child A or AB	126 "

The sedimentation of *compatible* cord red cells in P V P medium conformed to a rhythm which was the same in all blood samples examined the fall of 5 mm in 10 minutes, chosen as an arbitrary reference, continued at the rate of 5 mm every 5 minutes, and packing was not complete after $1^1/_2$–2 hours The same sedimentation rate was observed in compatible blood of premature children and those with obstetric complications, and even those who died a short time before labour or during labour

The sedimentation of *incompatible* cord red cells, on the other hand, varied greatly from one sample to another, and striking differences were seen most easily by simultaneous observation of a series of tubes Between a normal range and a much-hastened sedimentation-rate there was a whole range of intermediate rates which by means of the 10-min and 15-min readings could be divided into three categories



Sedimentation of four samples of cord-blood erythrocytes in P V P medium after 10 minutes Tube 1 child with ABO hæmolytic disease (case C, table I) tubes 2-4, healthy group-A children of group-O mothers

1 *Greatly accelerated sedimentation* —The fall of the red cells was most dramatic. After 10 minutes the column of clear supernatant fluid amounted to 90 mm. or more The erythrocytes packed at the bottom of the tube were clearly delineated from the supernatant liquid, in which only a few unagglomerated cells persisted. 10-minute readings of blood from group-A children of group-O mothers are shown in the accompanying figure Tube 1 contained the blood of an infant with hæmolytic disease (case C, table I) and it contrasts sharply with tubes 2-4, containing blood of healthy infants

Such a much-accelerated sedimentation-rate has been found in only 8 out of 835 incompatible cord bloods, all 8 were of mother O/child A

2 *Moderately accelerated sedimentation* —The 10-min readings did not show a clear delineation between the packed cells and those remaining in suspension The supernatant liquid became transparent gradually, the density of the red cells increased progressively from top to bottom, and at the lower extremity of the supernatant fluid small clusters of agglomerated erythrocytes could be seen distinctly with the aid of a lens In contrast, the 15-min. reading showed a massive red-cell deposit separated from the supernatant by a neat line of demarcation.

Such a type of sedimentation was found in 25 out of 835 incompatible cord bloods—23 times in the combination of mother O/child A, and twice in the combination of mother O/child B

3 *Normal or slightly accelerated sedimentation*—In this category we have included all cases in which the 15-min. readings showed no important sedimentation, such as a compact layer of red cells separated by a neat demarcation line at least 85 mm. below the upper limit of the tube

In many cases incompatible cord red cells did not settle more quickly than compatible ones In compatible ABO children affected by Rh hæmolytic disease the sedimentation of cord erythrocytes in P V P medium was not distinctly modified out of 20 cases we found 17 normal sedimentation-rates, and in the other 3 cases the sedimentation-rate was very slightly accelerated (20 mm at 15-min. readings instead of 10 mm as in normal ABO compatible children)

In each of the 8 cases where the cord-E S R. in P V P was strongly increased the child had severe hæmolytic disease. 4 of them showed both early anæmia and high indirect bilirubin levels, and underwent exchange-transfusions In 1 case anæmia (Hb 11 5 g per 100 ml) and hyperbilirubinæmia (17 mg per 100 ml) existed in a child 5 days old, at which age the infant left the clinic with its mother, who refused treatment In 2 cases the indirect bilirubin never reached a dangerous level, but the children had to be transfused with group-O packed

TABLE I—DATA CONCERNING 8 CHILDREN WITH GREATLY INCREASED SEDIMENTATION-RATE OF CORD CELLS IN P V P MEDIUM (ALL CHILDREN GROUP A, MOTHERS GROUP O)

Case	Maternal anti-A antibody at delivery			E.S.R. of cord cells in P.V.P. medium (mm.)		Osmotic fragility Hæmolysis *		Clinical condition of infant and treatment	Previous family history
	Saline	Human AB serum 37 C	Hæmolysin	10 min.	15 min.	Initial	Complete		
A	128	1024	4	104	108	0 62	0·42	Full-term, 3 120 kg early jaundice and anæmia 2 exchange-transfusions	Primipara
B	128	1024	8	130	132	0·62	0·42	Premature 7½ months, 2 520 kg , early jaundice and anæmia, 1 exchange-transfusion	8 previous children (group unknown) unaffected (?), 3 miscarriages
C	512	16,000	32	105	118	0·65	0 45	Full-term, 3 460 kg early jaundice and anæmia 1 exchange-transfusion child died at 1 month (cardiac malformation)	2 first children A_1 unaffected, 3rd dead at birth 4th A_1, exchange-transfusion 5th A_1 affected and transfused, 1 miscarriage
D	256	4096	4	100	118	0·65	0 38	Full-term 2 620 kg early jaundice and anæmia, transfusion of packed cells	Primipara
E	256	512	1	96	100	0·65	0 42	Full term, 3 560 kg , early jaundice and anæmia, transfusion of packed cells	1st child (group unknown) unaffected, 2nd A_1 early jaundice not treated
F	1024	8192	8	87	92	0·52	0 35	Full term, 3 500 kg early jaundice and anæmia left clinic at 5 days without treatment	Primipara
G	512	2048	2	97	110	0 55	0 35	Full-term, 3 590 kg early jaundice and anæmia 1 exchange-transfusion	1st child A_1 unaffected
H	128	512	2	85	110	0 55	0 35	Full-term 3 880 kg. no jaundice or anæmia until 5th day late anæmia (1 month) treated by transfusion	1st child group O unaffected

* Normal range with our technique in phosphate buffered saline initial hæmolysis 0·50–0·55, complete hæmolysis 0 30–0 35

TABLE II—INCIDENCE OF NEONATAL JAUNDICE IN 3924 INFANTS

Blood-groups	Sedimentation of cord red cells in P V P medium	No of cases	No jaundice	Slight jaundice	Deep jaundice	Exchange transfusion
Mother O, child A	Greatly accelerated	8	1	0	7	4 (twice in 1 case, see table I)
	Moderately accelerated	23	4	4	15	1
	Normal or slightly accelerated	385	*241*	*121*	23	0
Mother O, child B	Moderately accelerated	2	0	0	2	0
	Normal or slightly accelerated	145	91	44	10	0
Mother A, child B or AB	Normal or slightly accelerated	146	96	12	8	0
Mother B, child A or AB	Normal or slightly accelerated	126	82	37	7	0
Compatible children		3089	2039	886	164	1 (full term infant)
Total		3924	2554	1134	236	6

cells in the first week of life to correct anæmia In 1 case no anæmia or jaundice was observed until the child had left the clinic (5 days), but at the age of a month the child was admitted to a children's hospital with anæmia The data concerning these 8 cases are summarised in table I

In the 25 cases where the sedimentation-rate was moderately increased, the incidence of deep jaundice was very high (17 cases out of 25), and no anæmia was noticed, 16 of the children recovered without special treatment, although in 11 cases the indirect bilirubin reached very high, but not dangerous, levels In 1 case an exchange-transfusion had to be performed at the 4th day on account of hyperbilirubinæmia Of the 8 remaining cases slight jaundice was observed in 4, but serum-bilirubin was not measured

Among all other cases of ABO incompatible infants whose cord-erythrocytes showed a normal or slightly accelerated sedimentation in P V P medium the incidence of deep jaundice was not significantly greater than in the control group of ABO compatible children (table II) In this last group, 1 full-term infant had to undergo an exchange-transfusion on account of hyperbilirubinæmia of undetermined origin

Discussion

The phenomenon described here is the outcome of several years' research concerning ABO hæmolytic disease of the newborn and, principally, the means of early diagnosis We have studied most of the tests evolved for this purpose, all have been found disappointing In our experience, the hæmatological anomalies—i e, anæmia, high reticulocytosis, microspherocytosis, and increased osmotic fragility of the cord-erythrocytes—are very frequently absent in affected children By contrast, immunological tests are very often positive in perfectly healthy infants, especially in group A or B infants whose O mothers have a high-titred incompatible antibody Rosenfield's (1955) modified Coombs' test and the agglutination of cord-erythrocytes in macromolecular media is so often positive (sometimes quite strongly) in infants without jaundice that these tests cannot be taken into practical account Moreover, in healthy infants the presence of incompatible maternal antibody free in the cord serum *and* attached to the cord-erythrocytes, which give it up by elution, is sometimes observed, thus proving that the passage of incompatible antibody across the placenta and even its fixation on the child's red cells does not by itself always give rise to hæmolytic disease Something else must occur—perhaps modifications of the cell surface which manifest themselves in the agglutination of the erythrocytes in macromolecular media Such modifications do not seem to be a constant consequence of fixation of antibody on A or B cells The effect of such modifications is generally not deleterious for the red corpuscles, unless they reach a great intensity, and the intensity is not necessarily proportional to the amount of antibody fixed

Unfortunately, this intensity cannot be determined by a slide agglutination test We have tried to measure it by means of the sedimentation-rate, just as the intensity of rouleaux-formation of erythrocytes in their own plasma is measured by this technique The results, reported here, are very *promising* In all cases where the sedimentation-rate was greatly accelerated the children had severe hæmolytic disease, with anæmia and with or without hyperbilirubinæmia In cases with a moderately increased sedimentation-rate hyperbilirubinæmia was quite common, but this was not associated with anæmia and in our series required no special treatment, except in 1 case, moreover, in certain of these cases no jaundice was observed, so probably the immunological process played only a subsidiary role in the genesis of the disease In the cases where the cord-red-cells' sedimentation-rate was normal or only slightly increased, the incidence of deep jaundice was not significantly greater than in the compatible children In such cases when jaundice occurs the incompatibility plays probably a very small role, if any, whatever the nature and titre of maternal antibody

The phenomenon described here is observed only in hæmolytic disease due to ABO incompatibility The cord-red-cells' sedimentation-rate is normal or only very slightly increased in even severe Rh hæmolytic disease in ABO compatible children, showing that in this disorder the cellular modifications are quite different This difference of behaviour of cord-erythrocytes in ABO and Rh hæmolytic disease was observed by Munk-Andersen (1958) with his dextran/human-serum medium

A more detailed report of our work on ABO hæmolytic disease will appear elsewhere

Summary

The sedimentation-rate of washed cord erythrocytes suspended in a P V P medium was found to be greatly increased in severe ABO hæmolytic disease, and moderately but distinctly increased in most of the less severe cases

This phenomenon may prove useful in the study of cell changes in ABO hæmolytic disease of the newborn

We wish to thank Prof M Mayer and Dr P Walter, obstetricians, Saint-Antoine and Rothschild Hospitals, and Dr P Ducas, pædiatrician, Saint-Antoine Hospital, for their cooperation and interest We are grateful to the midwifery staff at both hospitals—especially to Miss A Dinovetzky for the collection of cord blood samples

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SURGICAL RELIEF OF SEVERE PARALYTIC HIP CONTRACTURE

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THIS paper reports favourable results of an attempt to relieve the severely crippling deformity of the hip which follows untreated anterior poliomyelitis in Uganda. The appearance of a child so afflicted suggests the need for extensive surgery involving many operations over a long period. Because most of these cases are in countries where neither hospital beds nor operating facilities suffice for this type of treatment, the children are left alone. They grow up as helpless cripples, with the prospect of only a short miserable existence, without schooling and without any hope of earning a living except by begging. If the child can be enabled to walk upright he can be sent to school and thus become a useful member of society. The procedure to be described reduces bed-occupancy and operating-time to a minimum, and can be followed wherever there is basic medical equipment. Its simplicity will appeal to those in medical charge of isolated hospitals in underdeveloped countries. Its effectiveness may lead to a reappraisal of the need for the major operations which form the orthodox treatment in orthopædic centres.

A child may be brought for advice because of a limp due to mild flexion deformity of the hip-joint after an attack of anterior poliomyelitis. Full flexion of the contralateral hip-joint eliminates lumbar lordosis and often reveals a greater degree of contracture than was at first expected. More often gross deformity is present (fig. 1), and the child is unable to walk, but crawls on all fours, or sits crouching in a fixed " tailor's position." The hips are then flexed, externally rotated, and abducted, the knees are flexed, and the feet plantar flexed.

Before a child in this condition can be taught to walk upright with crutches and callipers, various problems must be overcome. Deformity at the knee can be corrected by repeated manipulations and plasters. Subcutaneous tenotomy of the tendo Achillis (White 1943, Cummins et al. 1946) will relieve fixed plantar flexion. No equally simple method of relieving flexion contracture at the hip has been found in the literature.

The operation described by Campbell (1923), and since modified in many ways, is a major procedure involving detachment of the glutei from the ilium, and open division of all structures anterior to the hip joint. The contracture is effectively overcome, but apart from the time taken in the theatre over an extensive dissection, there are several disadvantages. Because it is a major procedure it is impracticable for both sides to be treated at the same time in bilateral cases, even if blood-transfusion is available. A full plaster spica is invariably required, and the stay in hospital lasts several months while repeated operations are also performed on the knees and ankles. The approach to the hip results in all the muscles around the joint being either detached from their origins or divided, whether they are paralysed or merely contracted. After operation the hip thus tends to become flail and unstable. For this reason greater difficulty has been experienced in training a child to walk after this operation than after the simpler procedure described below.

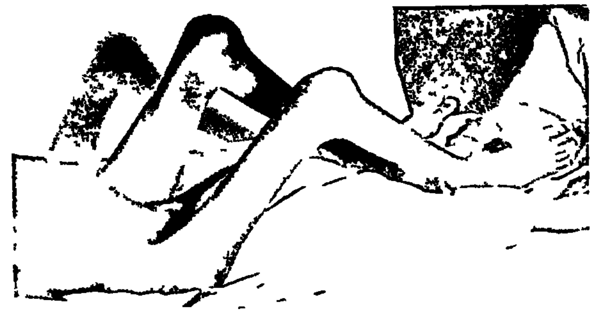

Fig. 1—Severe contracture of knees and hips in boy of 9 years, unable to do more than sit at home during past four years.

In February, 1958, Mr. Robert Roaf demonstrated a method he had developed in India when facing problems similar to our own. The basis of his operation was multiple subcutaneous division of the fascia lata. Successful application of this method depends on an understanding of the factors causing deformity in late poliomyelitis. The following analysis is based upon experience in treating 286 patients with varying types of paralysis of the lower limbs.

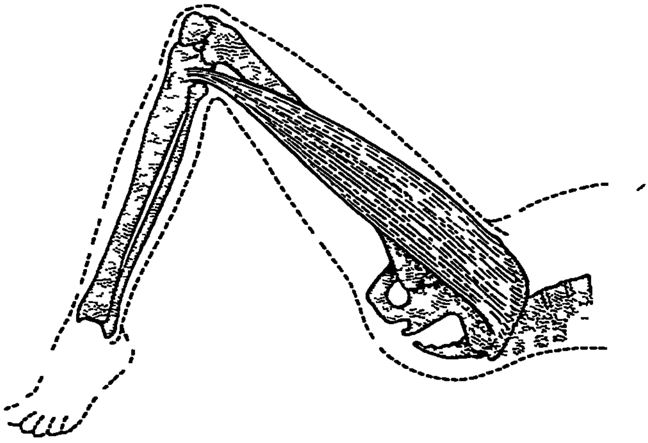

Fig. 2—Diagram showing effect of shortened iliotibial tract on knee- and hip-joints.

How Deformity is Produced

The deforming forces are multiple, but may be divided into those which begin to operate soon after the onset of paralysis, and those which later perpetuate the deformity.

The *initial deforming force* is the loss of balance between the paralysed muscles and their antagonists. Thus in the hip region the gluteus maximus and hamstrings are often paralysed, whereas the iliopsoas escapes, drawing the thigh up into a flexed position, or there may be loss of adductor power with continued action of the gluteus medius causing abduction. Loss of the glutei together with adoption of the squatting posture will result in external rotation at the hip.

The *later deforming force* results from the propensity of collagen fibres to shorten, taking up the slack between two points of attachment. This force is inherent in the following structures relevant to the hip:

(1) The fascia lata of the iliotibial tract will shorten as its point of attachment on tibia and crest of ilium come closer together. The tract stays as a rigid band and cannot be stretched by any manipulative force alone (fig. 2).

(2) Unopposed intact muscles will shorten and may need considerable force applied over a long period to stretch them out to their normal length. Iliopsoas muscle is the most important example of this.

(3) A paralysed muscle may be overstretched, undergoing fibre atrophy and dense interstitial fibrosis.

Roaf's Operation

Underlying Principles

The type of operative correction to be described avoids interference with normal tissues and deals with the deforming forces as follows

(1) The shortened fibres of the iliotibial tract, together with its deep attachments to the femur, are divided at several points along the lateral aspect of the thigh (fig 3) This releases contracted tissues which are strung across at some distance from the flexed hip-joint It also allows the knee-joint to be extended, so that relaxation of the quadriceps extensor permits further correction at the hip

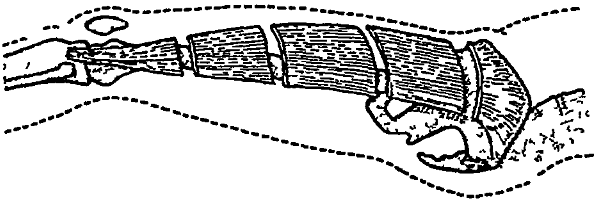

Fig 3—Diagram showing effect of operative division of shortened iliotibial tract

(2) The hip can then be extended by gradually stretching the shortened iliopsoas muscle, and the joint capsule These structures, in intimate contact with the bony surfaces, can later be stretched gradually by leverage upon the femur In most cases, extension exercises alone will suffice after operation In very severe cases stretching under anæsthesia and plaster-spica fixation may be required at intervals of about ten days until full correction is attained

(3) Hip extension allows stretched paralysed muscle (e g, gluteus maximus) to assume normal length, and thus to utilise any surviving motor units This may be the reason for an increase of muscle power which sometimes appears after severe deformity is corrected

Details of Operation

The patient is given a general anæsthetic and the affected hip and knee are extended as fully as possible The opposite hip is flexed to eliminate lumbar lordosis A tenotomy knife is introduced at four or five points along the lateral surface of the thigh, the first proximal to the knee-joint At each of these points the blade is pressed against the tensed fascia lata, then through the underlying fibrous tissue sheaths and septa of the (usually paralysed) vastus lateralis muscle until the bone is reached As these fibrous structures are divided, both the knee and the hip joints can be extended progressively

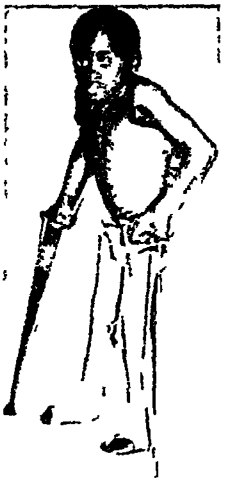

Fig 4

Fig 5

Fig 4—Patient in fig 1 four weeks after operation Hip spica has been removed and correction is almost complete

Fig 5—Same patient at home wearing callipers and now one of the family again

The femoral vessels are then palpated and guarded by a finger A tenotomy incision is made, 1 cm distal to the anterior superior iliac spine The knife is passed medially parallel to the inguinal ligament until the point lies beneath the skin lateral to the femoral sheath The blade is then pressed deeply against the tensed fibres of the fascia lata as they stand out under the skin The origins of sartorius and tensor fasciæ latæ (enclosed within the fascia) are usually divided at the same time, but the knife does not reach as deeply as the capsule of the joint or the tendon of iliopsoas

Bleeding from division of the superficial iliac circumflex artery may be brisk, but can be checked by firm pressure maintained for a few minutes The knife is then withdrawn and reinserted at the same place, the point now directed posteriorly The blade is pressed medially against the remaining fibres of the fascia lata as they pass over the glutei (medius and minimus) The tendons of these glutei are detached from the greater trochanter via a separate incision only if gross abduction deformity is present Minor degrees of abduction deformity at the hip assist in stabilising the pelvis while walking

A plaster cast is applied to the leg as its weight assists in maintaining extension of the hip, and later provides a temporary support for walking exercises When both hips have been treated in this way, the two plaster cylinders are sometimes bridged by a bar of plaster which checks external rotation and prevents the child from lying on his side with the hips flexed The physiotherapist visits daily, and by gentle passive extension of the hip completes the correction of any deformity remaining after the operation The child is nursed throughout either flat on his face or on his back

The most severe degrees of flexion deformity cannot be corrected in this way alone, because of the bowstring effect of the femoral neurovascular bundle across the flexed hip After operation, therefore, the hip is extended as far as the soft tissues allow, and a plaster spica is applied This plaster is either wedged or changed at intervals of ten days, until full correction is achieved (fig 4)

After operation, even in bilateral cases, there is relatively little pain, and some of the younger children are able to start walking by the side of their beds within two or three days In a fully corrected limb, the plaster is removed some fourteen days after operation, and the child is fitted with boots and simple adjustable length callipers (Burkitt 1959)

Results

So far 32 children have had either one or both their hip contractures relieved by this method Over the past eighteen months of continued observation there has been no relapse, although in some instances callipers had been temporarily discarded Once taught to walk, most of the children became determined to remain upright, and they were helped to attend local schools (fig 5) Regular visits were made to their homes to ensure that their boots, callipers, and crutches were maintained in good condition and changed when necessary This service is an essential supplement to the operation

An unexpected result of the operation (performed mainly for deformity of the hip) has been the ease whereby associated flexion contracture at the knee has been relieved None of the 32 patients so far treated have required osteotomy or open capsulotomy of the knee-joint, even though the original deformity has in some instances been over 90 of fixed flexion Division of the fascia lata therefore removes a deforming force which acts on both joints, as shown in figs 2 and 3

Apart from minor local hæmatoma, only 1 of the children treated in this way has suffered postoperative complications A child of 3 years, known to be suffering from sickle-cell anæmia, had a crisis after operation, but later recovered and became ambulant

Conclusions and Summary

The operation of multiple subcutaneous division of the fascia lata has enabled 32 African children with hip contractures to walk

Major surgery in all these cases has been avoided and interference in the routine of a busy general hospital has been slight

The operation has been only a phase in the management of each patient. Walking instruction, fitting and maintenance of callipers, and home visiting have also been necessary

It is hoped that a wider application of this method will enable paralysed children to become ambulant in those countries where they have hitherto been considered beyond the scope of surgical aid.

The procedure we have described offers certain theoretical and practical advantages over the more extensive operations at present accepted as the recognised orthopædic treatment for contracture of the hip

This investigation has been made possible by the enthusiasm and generosity of the Kampala Round Table, whose members have organised and financed the poliomyelitis clinic at Mulago Hospital.

Our thanks are also due to Prof I W J McAdam for his guidance and advice, to Mr Peter Cull for the illustrations, and to Mr Robert Roaf for his permission to describe a method which he originated himself

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RECURRENT HEPATIC COMA TREATED BY COLECTOMY AND ILEORECTAL ANASTOMOSIS

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THE neuropsychiatric manifestations of liver disease are believed to result from cerebral damage caused by nitrogenous substances formed in the gastrointestinal tract, which normally are removed by the liver and do not enter the general circulation in quantity Hepatic damage may allow these nitrogenous substances to reach the brain, either by passing through the damaged liver, or by circumventing the liver through portosystemic collateral channels which have developed as a result of portal venous obstruction (Kirk 1936) Portocaval anastomosis, which forms such a shunt, is not infrequently followed by neuropsychiatric disturbance (McDermot and Adams 1954), and Riddell (1955) placed the incidence of this complication as high as 10% after shunt operations

As the offending substances are formed from ingested protein by bacterial action in the intestine, symptoms are often controlled by restriction of protein in the diet and by antibiotics, such as neomycin, which reduce or modify intestinal bacterial activity Although usually remarkably effective, this regimen has certain disadvantages, in some patients protein restriction may have to be carried to the point of nutritional impairment, which in turn may lead to hypoproteinæmia with œdema and ascites Prolonged administration of broad-spectrum antibiotics may cause gastrointestinal disturbance and intercurrent infection with resistant staphylococci or yeasts

In the case described here these measures failed to prevent recurrent attacks of hepatic coma and led to gradual deterioration of the nutritional state. The problem of reducing intestinal bacterial activity to a minimum was solved by performing colectomy with ileorectal anastomosis, after which no further episodes of stupor or coma occurred and the patient tolerated a normal diet, thus enabling undernutrition to be corrected

Case-record

A housewife had had recurrent hæmatemeses from the age of 55 After the fifth episode of gastrointestinal bleeding, at the age of 63, she was transferred to Leeds General Infirmary and was noted to have hepatosplenomegaly and a few spider nævi on the face. She had never had jaundice or fluid retention and had always been mentally clear Portal venography revealed patent splenic and portal veins with extensive gastric and œsophageal varices Side-to-side portocaval anastomosis was performed by Mr J A. Aylwin on Aug 19, 1954 At operation the liver was noted to be grossly nodular The patency of the anastomosis was confirmed by portal venography two weeks after operation, and the intrasplenic pressure fell to within normal limits (12 mm. Hg)

Two days after operation the patient suddenly became confused and violent for twenty-four hours Three weeks later confusion recurred together with irregular coarse tremor of the hands and fœtor hepaticus, followed within twenty-four hours by coma which responded to treatment with aureomycin and intragastric infusion of glucose.

Thereafter recurrent episodes of hepatic stupor and coma occurred, and during the five years following portocaval anastomosis forty such attacks were recorded, necessitating fifteen admissions to hospital, the longest period that the patient remained free from coma was fourteen weeks (fig 1) In each attack she responded to omission of protein from the diet, large doses of antibiotics (usually neomycin), and evacuation of the contents of the large intestine by enemas Between these episodes she showed a variable degree of confusion and tremor despite restriction of the protein intake to 40 g daily and, in the later years, continuous administration of neomycin. As a result of restricted diet her weight gradually declined, by 1959 she had lost more than 40 lb in weight since portocaval anastomosis (fig 1) and had developed ankle œdema.

Four times during the early part of 1959 the patient was admitted to hospital in hepatic coma, and on each occasion had been constipated for some days before admission. The response to treatment was noticeably slower than it had been in previous attacks, and apparently this was mainly due to

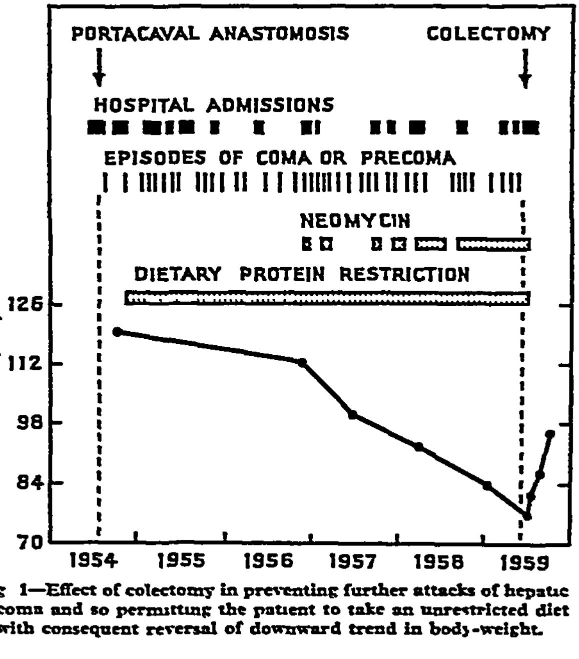

Fig 1—Effect of colectomy in preventing further attacks of hepatic coma and so permitting the patient to take an unrestricted diet with consequent reversal of downward trend in body-weight.

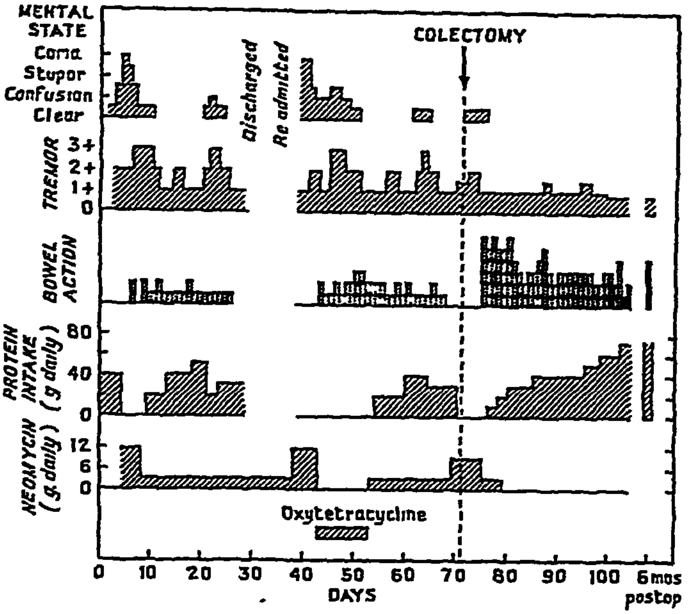

Fig 2—Effect of colectomy on protein tolerance assessed by changes in mental state and tremor

Before operation not more than 40 g of protein daily could be tolerated even when neomycin was taken. *After operation protein tolerance exceeded* 70 g daily and neomycin was not required

difficulty in emptying the bowel Repeated enemas were required to dislodge the hard fæces from the colon, but once these had been removed her neurological condition improved (fig 2)

As constipation appeared to play such a prominent part in precipitating hepatic coma and attempts to induce regular bowel habits with aperients and attention to diet had proved persistently ineffectual, it seemed justifiable to resort to surgical measures to correct this state of affairs, particularly as there were no other signs of impairment of liver function.

Colectomy with ileorectal anastomosis was performed on June 24, 1959 Exploration of the abdomen revealed a small fibrotic liver and a normal, rather visceroptosed colon. Total colectomy was carried out, with restoration of intestinal continuity by end-to-end anastomosis between the terminal ileum and the top of the rectum. Recovery after operation was entirely uneventful. Rather brisk diarrhœa in the immediate postoperative period soon gave way to more normal bowel function with about four loose stools daily and none at night. Hepatic coma or stupor have not recurred since colectomy, and the patient has shown progressive improvement in her mental state which is now clearer than at any time in the year preceding operation. Living alone she can manage her house and shopping without help Neomycin is no longer required and she can take an unrestricted diet. Consequently the downward trend in body-weight has been abruptly reversed and the ankle œdema has disappeared (fig 1) Fœtor hepaticus disappeared completely after operation and has not recurred

Some cerebral disturbance has persisted since the operation. Although well oriented in time and place and leading a moderately active life, the patient is emotionally labile and shows an inconstant tremor and dysarthria Two brief psychological tests, the Mill Hill Vocabulary Scale (1948) and Walton and Black's Modified Word Learning Test (1957) were administered by Mr R. G Webster six months after the operation Her score of 42 on the former places her in grade III minus, indicating an average verbal ability Her score of 31 plus on the latter test indicates that her capacity for word learning is impaired to a degree compatible with cerebral damage

Nitrogen Metabolism

Absorption of the products of protein digestion appeared to be unimpaired after colectomy because the fæcal nitrogen excretion was within normal limits (the mean daily value being 0·91 g over a six-day period)

Balance studies four months after operation, while the patient was on a protein intake of 60 g daily, showed a positive nitrogen balance

Protein Tolerance

During the preoperative period the protein tolerance was studied in relation to the neuropsychiatric state The mental state and tremor were assessed daily by the same observer During the period of observation regular bowel action was maintained by the use of aperients and neomycin was given. The results are shown in fig 2, where it will be seen that before operation on two separate occasions neurological deterioration started when the daily protein intake reached 40–50 g After colectomy the protein intake was gradually increased to the maximum the patient could eat (70 g), without untoward effect even though neomycin therapy had been discontinued

Fasting Blood-ammonia Levels

These were determined on peripheral venous blood by the method of Conway (1957) Five months before operation, on a day when the patient was in hepatic coma, the blood-ammonia was 3·0 µg ammonia-nitrogen per ml After maximum neurological improvement with medical treatment, the fasting blood-ammonia remained elevated and varied between 1·6 and 2·2 µg ammonia-nitrogen per ml., the mean level being 1·8

Five months after operation the fasting blood-ammonia had fallen to normal levels and varied between 0·7 and 1·1 with a mean of 0·9 µg ammonia-nitrogen per ml. This reduction in blood-ammonia, particularly as it occurred despite cessation of neomycin therapy and return to unrestricted diet *after* operation, strongly suggested that bacterial catabolic activity in the gut had been greatly reduced by colectomy

Methionine-tolerance Tests

Methionine, given orally, characteristically exacerbates the neuropsychiatric disturbance in patients with liver disease This action appears to be due to products formed by the breakdown of methionine by the bacteria of the gut, because it is abolished by preliminary suppression of the intestinal flora with broad-spectrum antibiotics, and parenteral methionine is non-toxic (Phear et al 1956) In our patient the

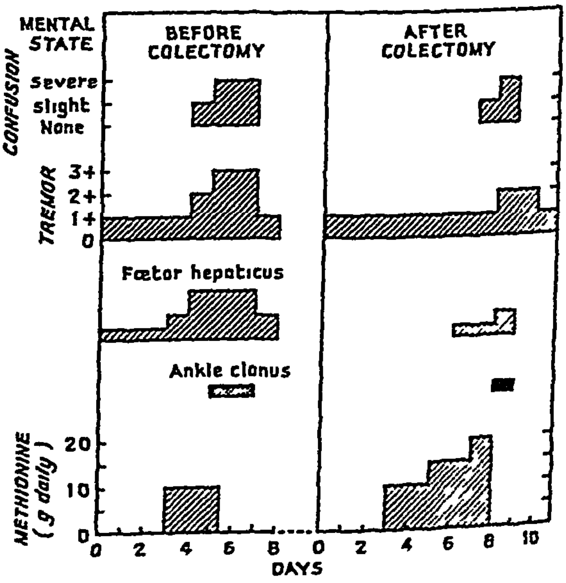

Fig 3—Influence of orally administered methionine upon neuropsychiatric state and fœtor hepaticus before and after colectomy After operation methionine tolerance was considerably improved

liability to develop neurological disturbance after methionine administration was used as an index of intestinal bacterial activity.

Before operation, at a time when symptoms were controlled by rigid dietary protein restriction alone, methionine was given by mouth in a dosage of 2·5 g. four times daily, and a daily examination was made to detect alteration in the neuropsychiatric state. On the third day of methionine administration, when the total dosage reached 25 g., mental confusion returned, tremor increased, and strong fœtor hepaticus developed (fig. 3). These rapidly improved when methionine was discontinued.

Five months after colectomy methionine tolerance was reassessed and was found to have improved greatly. Only after a total dosage of 75 g. did mental confusion occur together with increase in tremor and the appearance of fœtor hepaticus (fig. 3). The improvement in tolerance to oral methionine further confirmed that intestinal bacterial catabolic activity had greatly diminished after the operation.

Ammonium-tolerance Tests

A second and much less likely explanation of the fall in blood-ammonia levels and the improvement in methionine tolerance after operation is that liver-cell function improved about this time. This possibility seemed unlikely because the patient's response to oral ammonium chloride did not change. Before operation, when the neuropsychiatric state was controlled by dietary protein restriction and neomycin therapy, 2 g. of ammonium chloride three times daily caused obvious deterioration with return of mental confusion and increase of tremor on the second day, after a total dosage of 10 g. After operation ammonium chloride was given in a reduced dosage and similar deterioration was apparent on the third day, after a total of 9 g. The patient's ability to deal with ammonia absorbed from the gut was not increased after the operation.

Electroencephalographic Findings

The electroencephalographic pattern found in hepatic precoma or coma was described by Foley et al. (1950), Whitfield and Arnott (1951), and Bickford and Butt (1955). It has been correlated with the degree of neuropyschiatric disturbance (Parsons-Smith et al. 1957), the more severe this disturbance the greater the replacement of the alpha rhythm by slow theta and delta frequencies.

Electroencephalographic recordings were made four years, two years, and one week before colectomy, and two weeks, six weeks, and five months after colectomy. The preoperative records all showed typical changes with a dominant rhythm of 6–7 cycles per second bilaterally synchronous in the parieto-occipital and posterior temporal regions. An underlying alpha rhythm was still discernible. The earlier records were taken at times when the patient was grossly confused and precomatose, yet the record a week before colectomy, although taken after maximal improvement with medical treatment, showed no corresponding improvement in the electroencephalographic pattern.

The records taken after colectomy all showed persistence of the delta and theta frequencies, which were unchanged despite continued clinical improvement. Hence in this patient the electroencephalographic pattern did not appear to correlate with the degree of neuropsychiatric disturbance either before or after operation. Nevertheless, the persistence of such prominent electroencephalographic changes must be taken as confirming the clinical impression that some permanent cerebral damage has been sustained as a result of repeated attacks of hepatic stupor and coma before colectomy.

Discussion

In the early years of this century many clinical disorders were attributed to absorption into the general circulation of toxic substances produced by bacterial activity in the gut. Andrewes in 1913 stated "The main effect of bacterial activity in the production of alimentary toxæmia lies in their ability to carry out protein cleavages beyond the capacity of the ordinary digestive ferments . . . ", and Dixon (1913) mentioned ammonia and amines as such toxins normally dealt with by the liver. Arbuthnot Lane's (1909) application of colectomy to the treatment of the many diseases he ascribed to alimentary toxæmia resulting from "chronic intestinal stasis" aroused much controversy before this concept was eventually rejected. Amongst his patients was a woman unable to stand or walk and regarded as an imbecile who within a few weeks after colectomy, became happy, active, and intelligent (Lane 1912). The parallelism between this woman's case-history and that of our patient leads to the speculation that she had undiagnosed liver disease and therefore formed a counterpart to the present case.

In more recent years the susceptibility of patients with liver disease to neuropsychiatric disturbance when the dietary protein content is increased has been clearly recognised (Phillips et al. 1952, Sherlock et al. 1954), and the importance of bacterial activity in the gut in the formation of the offending nitrogenous toxins has been re-emphasised. The danger of constipation in precipitating symptoms, and the improvement which results from purgation, have been stressed by Dawson et al. (1957).

We have been unable to find previous reference to surgical treatment for colonic stasis in patients with neuropsychiatric complications of liver disease. Three operations were considered as a means to this end—simple terminal ileostomy, ileostomy combined with total proctocolectomy, and total colectomy with ileosigmoid or ileorectal anastomosis. Though either of the first two procedures might have been thought to offer a more certain prospect of eliminating intestinal stasis, they each had the serious drawback of involving the creation of an artificial anus, and the great attraction of the third operation was that it spared the patient this inconvenience. (This method was eventually favoured by Arbuthnot Lane [1909] in his surgical attack on intestinal stasis.) The occasion to perform colectomy in a patient without colonic disease had never hitherto arisen in our practice, but we had had considerable experience of colectomy and ileorectal anastomosis in the management of familial polyposis and selected cases of ulcerative colitis without rectal involvement. In such patients the operation is followed by mild chronic diarrhœa with normal anal continence, which is compatible with excellent general health and all ordinary activities. This operation was therefore chosen, and in the event has been followed by virtually no incapacity from frequent bowel actions.

Our observations emphasise that the products of protein digestion absorbed in the small intestine are not responsible for the cerebral disturbance in liver disease, after colectomy, despite the increased assimilation of protein, the neurological condition improved, thus clearly delineating the harmless and wholly beneficial process of protein digestion and absorption in the small gut from the potentially noxious one of bacterial degradation of the nitrogen residues reaching the large intestine.

Under normal conditions the bacterial content of the small gut is sparse (Cregan and Hayward 1953), but Martini et al. (1957) reported that in cirrhotic patients the flora of the ileum was increased and contained more coliform organisms and *Streptococcus fæcalis*. Conceivably our patient had an additional increase in ileal flora as a result of colonic stasis, and under these conditions relief of constipation by colectomy might in fact have reduced the bacterial content of the ileum The reduction in fasting blood-ammonia levels and the undoubted improvement in methionine tolerance both point to a drastic reduction in intestinal bacterial catabolic activity as a result of colectomy These findings could not be accounted for by a concomitant improvement in liver function, because the tolerance to administered ammonia remained unchanged after colectomy, and they strongly suggest that the clinical improvement was due to an overall reduction in the bacterial flora of the gut The ultimate prognosis in this patient may largely depend upon whether, and to what extent, the bacterial population of the small intestine increases in the future

The favourable results of colectomy in this patient suggest that this operation warrants a more extensive trial in patients with chronic or recurrent neuropsychiatric complications of liver disease It might be undertaken where medical measures have not controlled or prevented recurrence of symptoms, as in the present case Progressive undernutrition, resulting from prolonged restriction of dietary protein, might be taken as a second indication for colectomy, which, by increasing protein tolerance increases assimilation and thus improves nutritional status

Summary

Colectomy with ileorectal anastomosis controlled neuropsychiatric symptoms in a patient with recurrent attacks of hepatic stupor and coma, who five years previously had undergone portocaval anastomosis on account of portal cirrhosis with bleeding from varices

Protein tolerance was increased, and undernutrition, resulting from dietary protein restriction which had previously been necessary to diminish neuropsychiatric symptoms, was corrected

We are indebted to Dr M J Parsonage for the electroencephalographic studies, Mr R G Webster, M A, for psychological assessment of the patient after operation, and Miss Brenda Stannard for assistance with the blood-ammonia estimations

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“ It is now increasingly realized that a large part of the study of ‘handling human relationships’ is a generic study, that is, it is the same kind of study for doctors, teachers, social workers, and so on What these professional training courses share ought not to be just a string of helpful academic disciplines, an attempt at making some pious cultural contributions, to ensure that our professional worker is ‘well educated’ They ought to be integrated into a coherent course of study which could then represent the highest common factor of general education for all professional courses ”—PAUL HALMOS, *The Times*, Feb 15, 1960

HEPATIC COMA PRECIPITATED BY CHLOROTHIAZIDE IN HEPATIC CIRRHOSIS WITH ASCITES

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THE development of hepatic coma has been described previously in patients with cirrhosis after administration of nitrogenous substances by mouth (ammonium salts, ammonium cation-exchange resins, urea, methionine, and increased dietary protein) It has also been reported in patients given drugs such as acetazolamide, barbiturates, opiates, paraldehyde, and tranquillisers Severe infection, upper-gastrointestinal hæmorrhage, and abdominal paracentesis have also precipitated hepatic coma, and mercurial diuretics are believed to be capable of inducing coma

Here we report the production of hepatic coma in patients with hepatic cirrhosis and ascites who had been given chlorothiazide, a non-mercurial oral diuretic agent designated chemically as 6-chloro-7-sulphamyl-1,2,4-benzothiadiazine-1,1-dioxide

Material and Methods

Chlorothiazide, 1 g was given orally twice a day, at 8 A M and 2 P M, to 12 patients—8 males (7 adults and 1 child) and 4 females (2 adults and 2 children) with cirrhosis complicated by ascites and peripheral œdema A history of past hepatic precoma characterised by confusion, drowsiness, disturbed consciousness, and flapping tremor was obtained in only 1 instance (table I) The diagnosis of cirrhosis was established by a history of past jaundice (hepatitis) and poor food intake coupled with clinical and biochemical findings In doubtful cases the diagnosis was confirmed by liver biopsy

Ascites was graded as follows severe, tense ascites with cardiorespiratory embarrassment, moderate, tense ascites, and mild, slight ascites

All patients were given a salt-restricted diet, fluids were not restricted Urine was measured in twenty-four-hour amounts and saved for analysis Serum and urine were analysed for sodium and potassium by internal standard flame-photometry Serum and urine chloride concentrations were determined by silver-nitrate titration technique Diuretic response to chlorothiazide was assessed as follows excellent, œdema disappeared and no biochemical abnormalities or toxic effects developed, good, œdema disappeared but toxic effects or biochemical abnormalities developed, poor, œdema failed to clear completely or chlorothiazide was discontinued because of toxic effects or biochemical abnormalities

Only two stages of hepatic coma were differentiated impending coma (precoma), characterised by confusion, drowsiness, somnolence, and flapping tremor, and coma, characterised by violence requiring considerable restraint or unconsciousness with response only to painful stimuli or no response at all The regime of treatment in these patients consisted of (1) *withdrawal of chlorothiazide* (precipitating factor), (2) complete elimination of proteins from diet, (3) administration of oral antibiotics (tetracycline 2 g daily), (4) *removal of nitrogenous material in colon by enemas initially,* and subsequent administration of magnesium sulphate by mouth, (5) fluid and caloric requirements (at least 1500 calories per day) *supplied in the form of concentrated glucose* solution given as drinks, by intragastric drip, or intravenously, (6) vitamin (B complex) supplementation, (7) potassium chloride given orally 4 g daily (*caution was exercised especially* if the volume of urine was diminished), (8) good nursing care

TABLE I—CIRRHOTIC PATIENTS TREATED WITH CHLOROTHIAZIDE

Case no	Age (yr)	Sex	Past history of jaundice	Degree of ascites	Duration of ascites (mos)	Previous treatment	Serum-bilirubin (mg per 100 ml)	Serum-albumin (g per 100 ml)	Past hepatic precoma or coma
1	26	M	+	Severe	3½	Nil	1 8	2 2	–
2	22	M	+	Moderate	1½	”	0 5	3 1	–
3	25	M	+	”	3	”	1 5	2 7	–
4	40	F	+	Mild	1	”	0 8	3 5	–
5	42	F	+	Severe	2	”	2 6	2 7	+
6	38	M	–	”	6	”	1 2	2 5	–
7	30	M	–	”	3	”	2 0	2 2	–
8	35	M	–	”	9	Mercurials, paracentesis ×5	0 5	2 5	–
9	7	M	–	”	2	Nil	0 4	4·4	–
10	5	F	–	Moderate	1½	Mercurials	1 1	3 8	–
11	4	F	–	Severe	4	Nil	0 7	2 2	–
12	26	M	–	Moderate	6	”	0 5	3 2	–

"Recovery" from hepatic coma was defined as improvement sufficient for the patient to leave the hospital, or continued absence of coma or precoma so long as the patient remained in the hospital (average fifteen days)

Results

In 6 of the 12 patients the diuretic response was regarded as excellent (average weight loss 8 lb), in 2 as good (average weight loss 7 5 lb), and in 4 as poor (no weight loss) Chlorothiazide caused increased sodium, potassium, chloride, and urine excretion in all subjects, average twenty-four hour values during control and treatment periods are given in table II Increase in urinary potassium output was associated with a fall in serum-potassium level in every patient except case 9, who received potassium supplements of 2 g daily concurrently with chlorothiazide The increase in urinary potassium and the drop in serum-potassium level were usually most rapid and conspicuous in those having the greatest diuresis In cases 5 and 7, potassium excretion fell below control levels after cessation of drug administration, suggesting potassium depletion No major change in serum sodium and chloride concentrations was noted (table III) The fall in serum-potassium was associated with a slight fall in serum sodium and chloride values

Hypokalæmia, defined as a serum-potassium level below 3 mEq per litre, was noted in 4 patients receiving chlorothiazide without potassium supplements (table III) This state, although sometimes symptomless, is potentially dangerous

Hepatic Precoma and Coma

This syndrome was noted in 4 of the 12 patients treated (table II) It was usually associated with a good and rapid diuretic response to chlorothiazide

CASE 5 (fig 1)—A woman, aged 42 years, with cirrhosis of liver with ascites and jaundice was admitted to hospital with splenomegaly and severe ascites with ankle œdema There were no neuropsychiatric complications, hepatic fœtor, or flapping tremor, but there was a history of previous hepatic precoma. Chlorothiazide resulted in good diuresis (1800 ml of urine, compared with 120 ml. in control period) and 2 lb weight loss in two days However, within forty-eight hours after starting to take the drug, the patient became drowsy and had slight hepatic fœtor and flapping tremor The next day (fifty-eight hours after commencing the drug) she became violent, and extremely irritable and passed into a deep coma, regaining consciousness only after thirty-six hours of appropriate therapy

TABLE III—SERUM-ELECTROLYTES (MEQ PER LITRE) BEFORE AND FOLLOWING CHLOROTHIAZIDE 2 G DAILY

Case no	Before chlorothiazide			At completion of chlorothiazide			Duration of treatment (days)
	Na	K	Cl	Na	K	Cl	
1	135	4 2	100	133	2 7	98	14
2	145	5·0	100	134	4·0	90	6
3	137 5	4 1	110	130	3 8	104	8
4	133	4 7	98	134	4 2	98	4
5	135	4 2	98	126	2 8	95	2
6	130	4 0	96	128	3 8	96	6
7	136	4 8	102	128	2 5	98	2
8	128	4 5	103	128	4 0	102	7
9*	135	3 2	106	130	6 2	104	11
10	125	4 0	105	120	2 2	100	6
11	138	4 2	103	134	3 2	98	10
12	136	4 5	96	134	3 8	95	8

* Potassium chloride 2 g daily given concurrently with chlorothiazide.

CASE 7 (fig 2)—This man of 30 years, with cirrhosis with severe ascites and ankle œdema and no past history of jaundice or hepatic coma, responded to chlorothiazide with a good diuresis (1200 ml of urine compared with 150 ml in the control period) But within seventy-two hours after starting to take the drug the patient exhibited hepatic fœtor, flapping tremor, and confusion with severe irritability, and in the next twelve hours he became very violent, requiring considerable restraint and passed into deep coma, regaining consciousness only after a hundred and twenty hours of appropriate therapy

2 other patients (cases 1 and 10) exhibited hepatic precoma while receiving chlorothiazide

TABLE II—EFFECTS OF CHLOROTHIAZIDE 2 G DAILY ON URINE VOLUME AND ELECTROLYTES (MEQ PER TWENTY-FOUR HOURS) AND ON BODY-WEIGHT

Case no	Before chlorothiazide *				During chlorothiazide †							
	Na	K	Cl	Vol (ml /24 hr)	Na	K	Cl	Vol (ml /24 hr)	Duration of treatment (days)	Weight loss (lb)	Diuretic response	Complications
1	6 2	25	53	360	95	117	99	1510	14	10	G	Precoma
2	4 5	23	45	180	84 5	88 5	103	1800	6	8	E	
3	12	27	43	220	102	98 2	146	1200	8	0	P	
4	20	37	45	450	75	111 9	85	1500	4	2	E	
5	3	32	41	120	82	105	95	1800	2	2	P	Coma
6	1·4	10	50	130	90·5	75 5	107 5	1320	6	0	P	
7	8 2	45	55	150	108	145	117	1200	2	0	P	Coma
8	0 5	16	33	210	58	76	76 5	1800	7	12	E	
9	1 5	22	29	180	75		87	1600	11	9	E	
10	0 8	19	44	150	55	57	88	1530	6	5	G	Precoma
11	0 2	7 2	15	30	3·4	27 8	45	900	10	7	E	
12	6 5	27	55	180	137	127	165	2100	8	10	E	

* Mean of two days † Mean of first two days E = excellent G = good P = poor

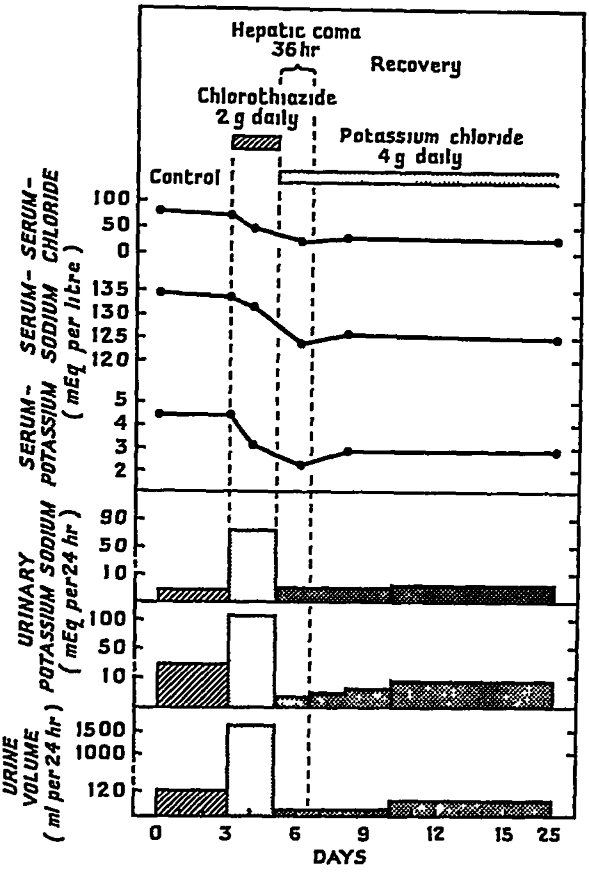

Fig 1—Findings in case 5

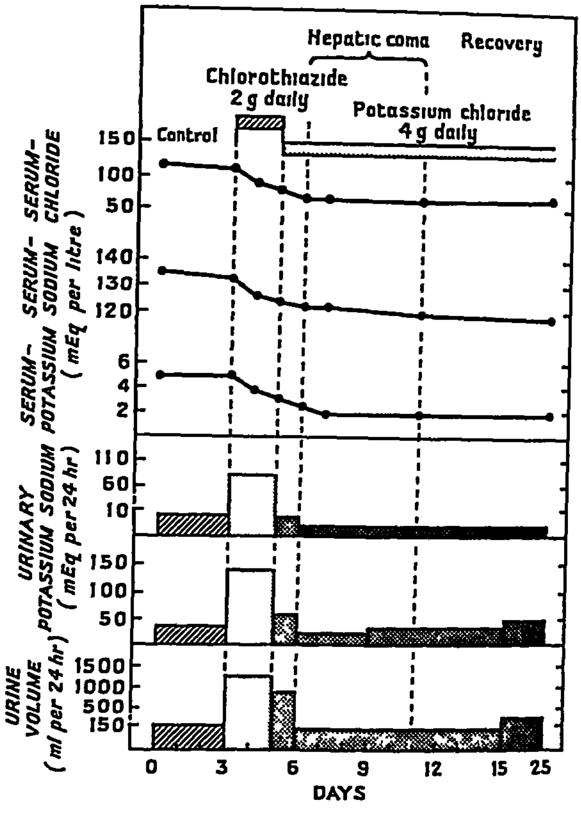

Fig 2—Findings in case 7
The hepatic coma lasted for 120 hours

Case 1 became drowsy and somnolent with numbness and tingling in the extremities He was relieved of these symptoms within twenty-four hours by potassium supplements (table iv)

Case 10 developed drowsiness which cleared up within thirty hours on administration of potassium supplements Measurements of serum albumin, bilirubin, cephalin-cholesterol flocculation, and thymol turbidity showed no alteration in liver function during and after chlorothiazide administration (table v)

TABLE IV—EFFECTS OF POTASSIUM SUPPLEMENTS ON SERUM-POTASSIUM IN CASES OF PRECOMA AND COMA

Case no	Duration of treatment (days)	Potassium-supplement (g /24 hr)	Serum-potassium	
			Before supplement	After supplement
1	4	3	2·7	3·9
5	5	4	2·8	4·0
7	8	2	2·5	3·8
9	6	2	3·2	6·2
10	5	2	2·2	3·5

Discussion

The results show that chlorothiazide can produce hepatic coma in cirrhotic patients with ascites The exact mechanism is not clear, but hypokalæmia and increased potassium excretion were a constant finding in the 4 present cases Hypokalæmia developing during administration of chlorothiazide to patients with cirrhosis and ascites has been observed by others Sherlock et al (1958) noted the development of hepatic coma during administration of chlorothiazide in 7 out of 13 patients with a previous history of this syndrome, and others have described 1 or 2 cases each In our series hepatic coma developed in 4 out of 12 cases and only 1 patient had a previous history of this syndrome It is our impression that the hepatic coma produced in these cases was related to hypokalæmia and potassium deficiency, since administration of potassium chloride caused clinical improvement in the 2 cases of hepatic coma (cases 5 and 7) and prevented further hypokalæmia and hepatic coma in the 2 cases of hepatic precoma (cases 1 and 10)

Conclusions

Chlorothiazide administered to 12 patients with cirrhosis and ascites produced impending or actual hepatic coma in 4 This was associated with increased sodium, potassium, and chloride excretion and a fall in serum-potassium concentration

Recovery from impending hepatic coma was obtained by oral administration of potassium chloride 4 g daily

Chlorothiazide is a useful diuretic agent in patients with

TABLE V—LIVER-FUNCTION TESTS BEFORE AND AFTER CHLOROTHIAZIDE ADMINISTRATION

Case no	Before chlorothiazide				After chlorothiazide			
	Serum albumin (g per 100 ml)	Serum-bilirubin (mg per 100 ml.)	Ceph chol flocc.	Thymol turb (units)	Serum-albumin (g per 100 ml)	Serum bilirubin (mg per 100 ml)	Ceph chol flocc	Thymol turb (units)
1	2·2	1·8	+ + − −	3	2·2	1·8	− − − −	3
5	2·7	2·6	− − − −	4	2·7	2·6	+ − − −	5
7	2·2	2·0	+ − − −	6	2·2	2·8	+ + + −	11
10	3·8	1·1	− + + −	14	3·8	1·1	− + + −	14

cirrhosis and ascites, but patients must be carefully observed for the development of hypokalæmia and hepatic coma

In our opinion chlorothiazide therapy should not be given to cirrhotic patients outside hospital—particularly patients with a past history of hepatic coma or precoma Potassium chloride supplements 2–4 g daily should be given to avoid hypokalæmia, and special caution should be exercised if the volume of urine is diminished

Unfortunately chlorothiazide therapy is particularly dangerous in the patients with the most satisfactory diuresis

We wish to thank Dr K B Kunwar and Dr M M Singh for their valuable help and advice in all the phases of this work, and Mr R. P Srivastva for his technical help We are grateful to Merck, Sharp & Dohme for a supply of chlorothiazide, and to Unichem Laboratories, Bombay, for a research scholarship awarded to one of us (S P S T)

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URINARY OSMOLALITY IN THIRSTING NORMAL SUBJECTS

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DETERMINATION of the specific gravity of the urine after a period of fluid deprivation has been widely used as an indirect indication of the concentrating-power of the kidney The osmometers now available enable workers to measure renal concentrating-power directly, in terms of osmotically active solute per litre of urine water With this method it was soon shown that urinary specific gravity is only roughly related to urinary osmolality (Miles et al 1954, Baldwin et al 1955, Isaacson 1959) But such studies of renal concentrating-power as now exist, measured in osmolar values, are few, involve small numbers of normal subjects, and have given differing results (Frank et al 1957, Boyarsky and Smith 1957, Dorhout Mees 1959) Accordingly, I have measured urinary osmolality in 63 apparently normal subjects, after an eighteen-hour period of fluid deprivation, in an attempt to supply definitive figures for this parameter of renal function

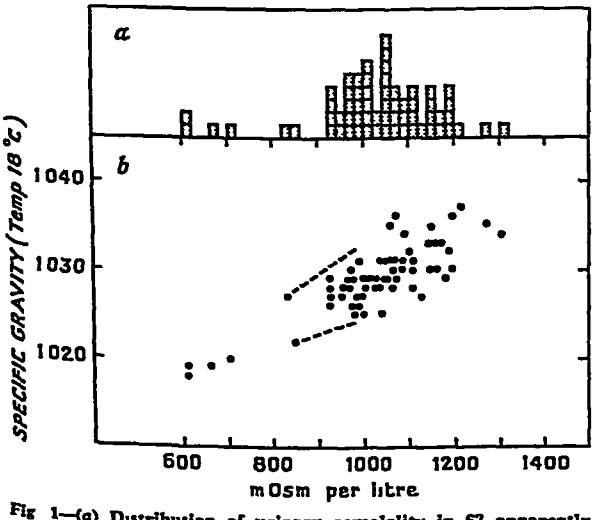

Fig 1—(*a*) Distribution of urinary osmolality in 63 apparently normal people, after eighteen hours fluid restriction Each square represents one person. (*b*) Relations between urinary osmolality and specific gravity in the concentrated urines of (*a*)

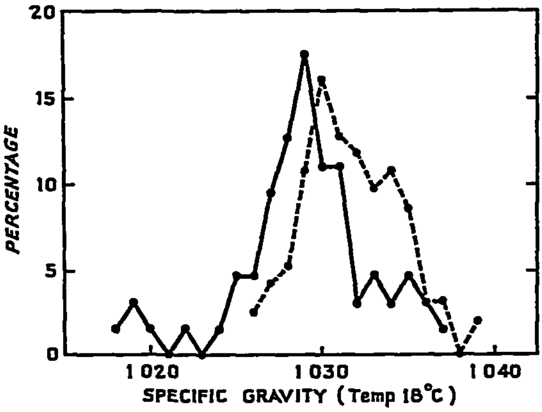

Fig 2—Distribution of specific gravity expressed as percentage of the number measured The dotted line represents a comparable series investigated by Addis and Shevky (1922)

63 medical students volunteered for the test. They were asked to abstain from all fluids or liquid foods from 12 NOON, to empty their bladders before going to bed, and to save a specimen of their early-morning urine next day They were to partake of their usual meals, without liquids, and to carry on with their usual activities Urinary specific gravity was determined with an ordinary clinical hydrometer, and osmolality with a Fiske osmometer, accurate to 1% All urine specimens were found to be free from sugar and protein

The results are shown in fig 1 57 (90%) of the students attained urinary osmolalities of over 900 milliosmols per litre The mean was 1027 mOsm (S D of 110 mOsm) The range was 610 to 1302 mOsm, 85% falling between 900 and 1200 mOsm

Different authorities give different levels for the urinary specific gravity which, after varying periods of dehydration, indicates adequate renal concentrating-power (see Fishberg 1954) Fig 1(*b*) shows that, while a rough correlation exists, the specific gravity may vary by as much as 0 006 for any given osmolality Urine concentrated to 900 mOsm per litre must have a specific gravity of at least 1 023, but only with specific gravity above 1 029 can one be sure that the urine has attained this osmolality

In 1922 Addis and Shevky recorded the range of urinary specific gravity in 75 normal subjects, after twenty-four hours' fluid deprivation Fig 2 shows the distribution of specific gravities obtained by me (expressed as percentages of the number measured) compared to that given by Addis and Shevky My adoption of eighteen hours' rather than twenty-four hours' fluid restriction resulted in slightly lower urinary concentrations From the known rough correlation between urinary specific gravity and osmolality, and the similarity of the curves in fig 2, we can infer that the range of osmotic concentration in the series studied by Addis and Shevky must have been very similar to, if somewhat higher than, that found in the present series

Summary

63 normal medical students were subjected to an eighteen-hour urine-concentration test Urinary concentrations of over 900 mOsm per litre were obtained in 90%, with a mean of 1027 mOsm (S D of 110 mOsm)

Concentrated urines show only a rough correlation between specific gravity and osmolality Urine of 900 mOsm per litre must have a specific gravity of at least

1·023, but only at a specific gravity of 1·029 can one be certain that the urine has attained this osmolality

My thanks are due to Dr L Eales, associate professor of medicine in the University of Cape Town, for helpful criticism and advice

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INTRACELLULAR pH OF POTASSIUM-DEFICIENT VOLUNTARY MUSCLE

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Cooke et al (1952) found that, during dietary potassium depletion in rats, the potassium leaving the muscle-cells was partially replaced by sodium, about 2 mEq of sodium passing into the cell for every 3 mEq of potassium passing out They postulated that the deficit of cation was corrected by hydrogen ions migrating into the cells, causing an extracellular alkalosis and an intracellular acidosis Black and Milne (1952) showed that extracellular alkalosis in experimental potassium depletion in man was not associated with increased loss of hydrogen ions from the body, and they suggested that the alkalosis was due to redistribution of hydrogen ions between the extracellular and intracellular spaces

Migration of hydrogen ions into muscle during potassium depletion should lower the intracellular pH, but actual measurements of the average pH of potassium-depleted muscle have given conflicting results Gardner et al (1952) and Schwartz and Wallace (1952) found that intracellular pH was reduced considerably in potassium depletion Darrow et al (1953) and Eckel et al (1959) reported that the pH was not reduced significantly below normal values All previous workers used a technique dependent on the distribution of free carbon dioxide and bicarbonate between plasma and muscle to which there are several theoretical objections and which is often inaccurate Waddell and Butler (1959) have introduced a method for determining muscle pH which is apparently more satisfactory, this is based on the distribution of a non-toxic weak acid—5 5-dimethyl-2 4-oxazolidinedione (D M O)—between plasma and muscle We have used this method to measure the intracellular pH of normal and potassium-depleted rat muscle and to confirm that in potassium deficiency the acidity of muscle-cells increases

Methods

Potassium depletion was produced in rats by the method described by Evans et al (1957), except that injections of deoxycortone acetate were not given A group of twenty two albino rats, weighing 100–200 g, were used experimentally, and twenty litter mates served as controls There were two differences between the experimental group and the controls In the experimental group cation-exchange resin in the sodium phase ('Resonium-A', Bayer) was added to the diet (30 g resin per kg of food), whereas the controls were not given resin but potassium salts (50 mEq per litre) were added to their drinking-water Plasma and muscle-cell pH was determined when the rats had had the experimental diet for 5–12 weeks

The method of Waddell and Butler (1959) for measuring muscle-cell pH was slightly modified as follows D M O 70 mg per kg body-weight and heparin 500–1000 units were injected intraperitoneally, and 3–4 hours was allowed for equilibration The rat was then rendered unconscious by a blow on the head and was bled immediately via a cervical incision, the blood being collected under liquid paraffin without any contact with air Blood pH was measured at 37°C by a glass electrode Muscle potassium and chloride were determined in 0·1 g and 0·5 g respectively of fat-free dry muscle solid prepared from voluntary muscles of the hind limbs

Statistical Analysis

Previous workers have regarded normal and potassium-depleted rats as two distinct groups, and have compared mean values from each group We applied this method of analysis in table I But in fact the potassium-depleted group was far from uniform, some rats being only mildly depleted of potassium and clinically healthy, others being obviously ill from severe potassium loss

The degree of deficiency is best measured by determination of the potassium content of muscle fat-free dry solid (F F D S) and this method of statistical analysis was used in table II and figs 1 and 2 The levels ranged from a high normal value of 475 µEq potassium per g F F D S to a grossly low value of 225 µEq potassium per g F F D S at the extreme of potassium depletion Thus plasma pH

TABLE I—STATISTICAL ANALYSIS OF MUSCLE-POTASSIUM, HYDROGEN-ION CONCENTRATION OF PLASMA AND INTRACELLULAR FLUID, AND HYDROGEN-ION GRADIENT IN NORMAL AND POTASSIUM-DEPLETED RATS

Comparison	Mean of normal rats	Mean of potassium-depleted rats	*t* value	*P*
Muscle-potassium (µEq per g F F D S)	447 (S D 18·1)	298 (S D = 38·2)	3·9	0·001
Hydrogen-ion concentration in intracellular fluid (moles per litre)	$11{\cdot}99 \times 10^{-8}$ (S D $3{\cdot}58 \times 10^{-8}$) (Mean pH = 6·92)	$20{\cdot}20 \times 10^{-8}$ (S D = $10{\cdot}36 \times 10^{-8}$) (Mean pH 6·69)	2·92	<0·01
Hydrogen-ion concentration in extracellular fluid (moles per litre)	$4{\cdot}05 \times 10^{-8}$ (S D $0{\cdot}195 \times 10^{-8}$) (Mean pH = 7·39)	$3{\cdot}16 \times 10^{-8}$ (S D $0{\cdot}216 \times 10^{-8}$) (Mean pH 7·50)	5·62	0·001
Hydrogen-ion gradient between intracellular and extracellular fluids (H_i/H_e)	2·96 (S D 0·89)	6·33 (S D 2·96)	3·8	0·001

TABLE II—STATISTICAL ANALYSIS OF THE RELATION BETWEEN HYDROGEN-ION CONCENTRATION OF PLASMA OR VOLUNTARY MUSCLE TO THE POTASSIUM CONTENT OF MUSCLE F F D S

Regression against potassium per g F.F.D S	Gradient of regression line	Significance of difference from zero gradient	Correlation coefficient	Significance of correlation
Extracellular pH	−0 0006	P<0 001	−0 82	P<0·001
Intracellular pH	0 0013	P<0 01	0 54	P<0·001
Hydrogen-ion concentration in extracellular fluid	$0{\cdot}0051 \times 10^{-8}$	P<0·001	0 81	P<0 001
Hydrogen-ion concentration in intracellular fluid	$-0\ 0404 \times 10^{-8}$	P<0 025	−0 35	P<0 02
H_i^+/H_e^+	−0 0216	P<0·001	−0 62	P<0 001
log H_i^+/H_e^-	−0 00194	P<0 001	−0 69	P<0 001

and muscle pH can be regarded as continuous variables dependent on the potassium content of the body

The statistical methods were those described in the monograph by Snedecor (1956)

Results

Table I shows that there was an extracellular alkalosis and an intracellular acidosis in the potassium-deficient rats, the mean plasma pH being 0 11 units above control values, and the mean muscle pH 0 23 units below control The hydrogen-ion gradient across the muscle-cell membrane was 2 2 times as great in the potassium-depleted as in the normal rats All these differences are highly significant statistically

Fig 1 shows a linear relation when both plasma pH and muscle pH are plotted against the potassium content of muscle F.F D S A more significant correlation is obtained if pH rather than hydrogen-ion concentration is plotted as ordinate, as shown in table II Since plasma pH rises and intracellular pH falls with increasing severity of potassium depletion, the hydrogen-ion gradient across the muscle-cell membrane becomes progressively greater with increasing potassium loss

In fig 2 the hydrogen-ion gradient between intracellular and extracellular fluids expressed logarithmically (log $[H_i^+/H_e^+]$) is plotted against the potassium content of muscle F F D S Again a much closer correlation is obtained if the logarithm of the gradient rather than the gradient itself is plotted as ordinate Table II shows that the gradients of the regression lines and the correlation coefficients are all significantly different from zero at a high degree of statistical probability

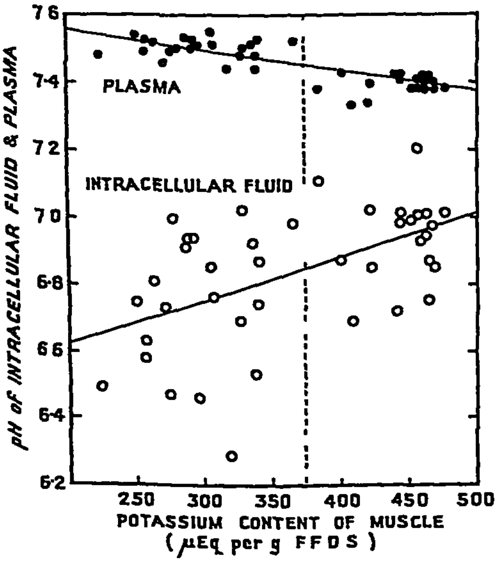

Fig 1—Relation between pH of intracellular fluid of muscle or plasma and potassium content of voluntary muscle

The continuous lines are calculated regression lines Values to the left of the broken line are from potassium-depleted rats, values to the right are from controls

The theoretical implication of these results will be discussed later in a more detailed paper This account merely presents the experimental data showing that, as postulated by many previous workers and denied by others, muscle from potassium-depleted rats is significantly more acid than normal muscle

Summary

A method, involving the distribution of the weak acid 5 5-dimethyl-2 4-oxazolidinedione was used to measure the intracellular pH of normal and potassium-depleted muscle in rats Potassium depletion caused significant extracellular alkalosis and intracellular acidosis, with an increased gradient of hydrogen ion across the muscle-cell membrane Better correlation with the degree of depletion was gained by using pH rather than the actual hydrogen-ion concentration, and the logarithm of the hydrogen-ion gradient rather than the hydrogen-ion gradient itself The mean pH of normal muscle was estimated at 6 92, and of potassium-depleted muscle at 6 69

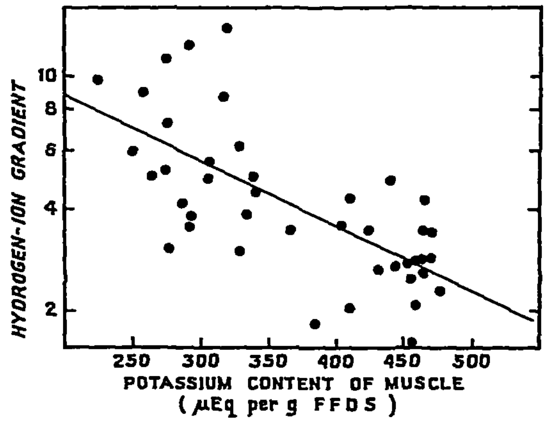

Fig 2—Relation between the hydrogen-ion gradient across the muscle-cell membrane and the potassium content of voluntary muscle in normal and potassium-depleted rats

The continuous line is the calculated regression line

Thanks are expressed to Boots Pure Drug Company, and especially to Dr J Warwick Buckler, for synthesis of a pure sample of 5 5-dimethyl-2 4-oxazolidinedione

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PHARYNGEAL POUCH TREATED BY DIVERTICULO-ŒSOPHAGOSTOMY

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PHARYNGEAL pouches are now usually treated by one-stage excision as advocated by Harrington (1945) When mediastinal infection was a more likely complication than it is today, invagination of the pouch was tried, in order to avoid opening the œsophagus (Bevan 1917), Hill (1917) suggested mobilising the pouch and suturing its distal end higher up the neck, to provide drainage from the sac into the œsophagus Neither of these two methods was widely adopted Two-stage excision, which was introduced by Goldmann (1908) and practised by Lahey (1940), was also performed in the hope that the complication of mediastinitis would be avoided More recently, diathermy excision of the septum between the pouch and the œsophagus, using a special œsophagoscope with a divided end, has been successfully carried out (Harrison 1956) When major surgery is contraindicated, and in the early stages of pouch formation, simple dilatation of the cricopharyngeal sphincter with an œsophagoscope may improve swallowing

We report a case in which a new operation has been tried for a very large pouch

Case-report

A man of 57, a hairdresser, presented with a five-year history of regurgitating food after meals, this symptom had become worse over the last year There was no spill-over into the larynx when he swallowed or at other times, and, although he had lost weight, his appetite was good and he remained at work He was thin (weight 107 lb) but there were no physical signs in the chest or neck Radiological investigations were made, and a barium swallow showed a very large pharyngeal pouch (fig 1)

Films taken during inspiration and expiration suggested that the pouch was adherent in the right side of the chest, films taken during a Valsalva manœuvre showed pharyngoceles (fig 2) There was also a congenital abnormality of the cervical spine, which showed fusion of the articular processes and the laminæ of the 5th and 6th vertebræ and narrowing of

Fig 2

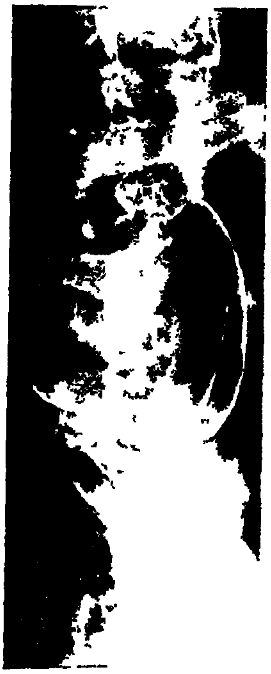
Fig 5

Fig 2—Anteroposterior view showing pouch and pharyngoceles during a Valsalva manœuvre

Fig 5—Barium swallow after operation, showing a satisfactorily functioning stoma

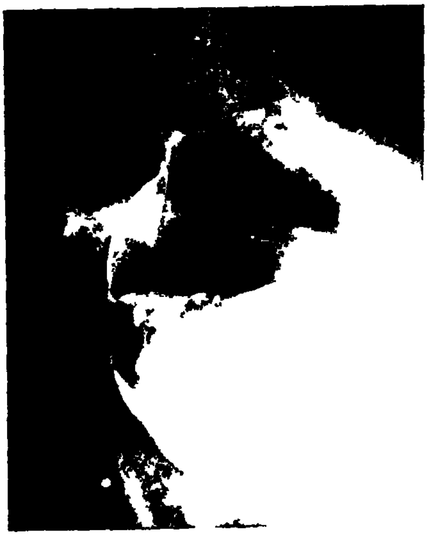
Fig 1

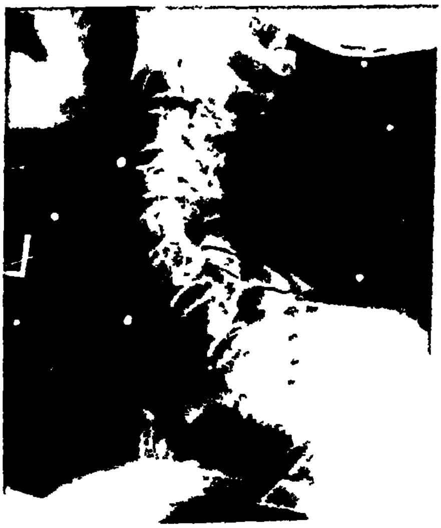
Fig 3

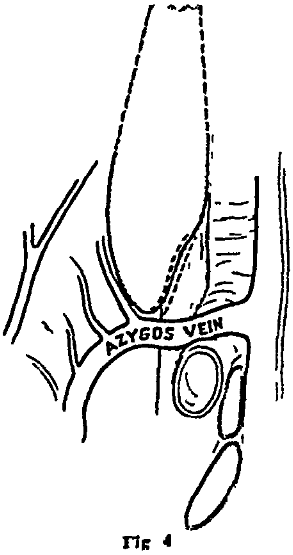

Fig 4

Fig 1—Lateral view of pharyngeal pouch containing barium

Fig 3—Lateral view of cervical spine, showing congenital abnormalities of the 5th and 6th vertebræ

Fig 4—Diagram of the right lateral view of the mediastinum showing the pouch extending down to the level of the tracheal bifurcation and the site of the anastomosis to the œsophagus

he disc between them (fig 3) At œsophagoscopy the instrument passed straight into the pouch, which was clean and howed no signs of inflammation. It was possible to move the esophagoscope about in the upper part of the chest in a remarkible way, and to see the vertebral column bulging into the ouch posteriorly, the opening of the pouch into the œsophagus ould not be found

When treatment came to be considered, it seemed nevitable that excision of the pouch would involve pening the chest and the neck, and though large pouches isually come up into the neck without difficulty, it was eared that this one might be adherent to a large vein One of us (R A W) therefore suggested that as a simpler lternative the lower end of the pouch should be anastomosed to the œsophagus in the chest This operation (diverticulo-œsophagostomy) was performed by Mr T Holmes Sellors on March 18, 1959

The chest was opened on the right side, along the upper border of the sixth rib, and after division of the azygos vein the pouch was easily identified, it extended downwards from the neck to the level of the tracheal bifurcation. An opening was made at the lowest point of the pouch (empty except for two green peas), and a vertical incision was made in the œsophagus at the same level. An anastomosis about $1\frac{1}{2}$ in. long was then made between the pouch and the œsophagus (fig 4) A Ryle's tube was passed through the pouch and lower œsophagus into the stomach, and the chest closed with drainage The postoperative course was uneventful and a fortnight later the patient was swallowing solids well and had gained 10 lb

Ten weeks after operation he reported that he was eating normally and had gained 27 lb Another barium swallow showed a satisfactory stoma between the pouch and the œsophagus (fig 5)

Summary

A large pharyngeal pouch was treated by anastomosis of its distal end to the œsophagus in the chest.

We are grateful to Mr C. P Wilson, Mr R. S Handley, and Mr T Holmes Sellors for permission to publish this case, to Mr A Turney for the photographs, and to Miss Hewland for help with the diagram

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Preliminary Communication

HEART-SPECIFIC AUTOANTIBODIES

SINCE the claims of Masugi [1] and Cavelti,[2] there have been a number of reports of the presence of circulating autoantibodies in cases of heart-disease,[3] [4] none of them, however, showing the heart-specificity of the autoantibodies found.[5] Recently, Kaplan indicated the existence of two anti-heart autoantibodies in rheumatic patients, with specificity toward heart tissue [6] There is some evidence of production of anti-heart antibodies in experimental animals [7] [8]

We report here the production of antibodies to heart-muscle antigen in animals, the activity and specificity of such antibodies, and their presence in sera of human beings with and without heart-disease

MATERIAL AND METHODS

Immunisation —A group of mongrel rabbits was given 6 weekly injections subcutaneously of a homogenate of pooled rabbit hearts mixed with Freund's adjuvant [9] A second group received injections of buffered saline extracts of rat heart with and without adjuvant.

Serology —Antigens were buffered saline extracts of minced organs Rabbit sera were examined by a modified Boyden's passive hæmagglutination technique (P H),[10] gel precipitation,[11] and complement-fixation tests Human sera were examined by the P.H technique, fresh or after storage at −20°C for varying periods

Pathological effects—Possible cytopathogenic effects of rabbit sera were examined on 4–5 days old tissue cultures of rabbit or rat heart explants in clot In addition, histological examinations were made on the various organs of immunised rabbits

RESULTS

Rabbits Immunised with Rabbit Heart (table I)

In the P H test, two out of four rabbits gave high titres (up to 1/2500) with autologous and homologous heart extracts Lower titres were obtained with extracts of other mammalian hearts (rat, guineapig, dog, and human) and chick heart extracts gave the lowest titres Extracts of other rabbit organs gave negative results

Absorption of sera with heart extracts caused reduction in P.H titre, while absorption with other organ extracts did not.

Preincubation of sera diluted to half the P.H. titre, with heart extracts, caused the inhibition of the P H with heart extracts (hæmagglutination inhibition or H.I test [12]) while extracts of rabbit lung, liver, and kidney did not show this effect.

TABLE I—REACTIONS OF SERA OF RABBITS IMMUNISED AGAINST RABBIT HEART

Extract	Passive hæmagglutination	Gel precipitation	H.I * with heart-sensitised erythrocytes
Rabbit heart	+	–	+
Other rabbit organs	0	+	0
Other mammalian heart	+	–	+

+ signifies positive result or, in last column, positive inhibition.
* Hæmagglutination-inhibition.

Complement-fixation tests showed only an insignificant rise in titre compared with preimmunised sera, while the gel-precipitation method gave positive results, both with heart extracts and with extracts of other rabbit and mammalian organs The reasons for this remain to be elucidated there is some evidence that these antibodies are different from the anti-heart antibody detected in the P H test.

Rabbits Immunised Against Heterologous Heart Extracts

In addition to anti-rat (species-specific) antibodies shown by all serological techniques used, all four rabbits of this group showed anti-heart (organ-specific) antibodies in their sera as revealed by the P.H. technique These antibodies reacted with autologous heart extracts as well as with those of other animals The non-identity of the two groups of antibodies is shown by the results of the H I test (table II) Antibodies to rat heart were inhibited by extracts of rat heart but not by extracts of other rat organs or other mammalian heart. Antibodies to " rat " were inhibited by all rat organs tested but not by other mammalian hearts, while " heart " antibodies were inhibited only by heart extracts

Pathogenic Actions

None of the sera of the immunised rabbits had a cytopathogenic action on rabbit heart cells in tissue culture. However, the sera of rabbits immunised against rat heart extract did have a cytopathogenic action on cultures of rat heart cells

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TABLE II—HÆMAGGLUTINATION-INHIBITION REACTIONS OF SERA OF RABBITS IMMUNISED AGAINST RAT HEART

Erythrocyte-sensitising extract	Inhibiting extract		
	Rat heart	Other rat organs	Other mammalian heart
Rat heart	+	0	0
Other rat organs	+	+	0
Other mammalian heart	+	0	+

+ signifies inhibition of hæmagglutination.

No pathological lesions were found in the hearts of rabbits immunised with homologous heart extract, although some showed circulating anti-heart autoantibodies

The rabbits immunised with the aid of adjuvant showed the focal infiltrations in lungs, liver, and brain ascribable to the adjuvant [13]

Three Groups of Human Sera

1 *A case of post-myocardial-infarction syndrome*—This is the Israel case referred to by Dressler [14] The serum had been stored at −20°C for 4 years In the P H test with human heart extract, there was a strong positive reaction up to a dilution of 1/160 and a titre of 1/80 with extracts of other mammalian hearts (dog, guineapig, rat, and rabbit) Extracts of human and rabbit kidney gave negative results in this test The specificity of these antibodies for heart was shown in the H.I test (table III)—i e., they were inhibited by extracts of mammalian heart but not by extracts of other organs

A second serum sample, taken after 4 years' freedom from attacks, was negative

2 *Adults in hospital with heart-disease*—These sera were examined fresh, against extracts of human and dog heart and human kidney

Three out of four cases of recent myocardial infarction and all of five cases of acute rheumatic activity (on a chronic background) gave positive results Of eight patients with myocardial insufficiency, anginal syndrome, and the like, five were positive

Only one of five cases of inactive rheumatic or congenital heart-disease was positive when examined immediately before or after cardiotomy This patient had had recurrent congestive heart-failure for some years

As a control, fifteen sera sent to the clinical laboratory for a variety of tests (e.g , rhesus group in pregnancy) were examined Two of these gave a positive P H test

All the positive sera reacted with both human and dog heart extracts Some of them reacted, too, with kidney extracts As in no case the titre was higher than 1/10, further characterisation of antibody specificity was not possible

3 *Children with non-active rheumatic heart-disease*—The sera had been taken up to 2 years previously from children in a communal settlement with a high prevalence of rheumatic heart-disease All the children had received continuous chemoprophylaxis and none had detectable albuminuria Nine out of twelve gave positive reactions similar to those described in the adults (group 2)

Of fourteen sera from apparently healthy children from the same settlement, four gave positive P H. tests

COMMENTS

It is hard to conceive of an autoimmune reaction that is not linked to a specific antigen, such as is involved in diseases of lens,[15] testis,[16] brain,[17] and thyroid [18] Among the few investigators successful in demonstrating autoantibodies in heart-disease, only Kaplan has shown their organ specificity [6,7] In his case, however, the antigen was particulate and insoluble in saline, unlike those described here

TABLE III—HÆMAGGLUTINATION-INHIBITION REACTIONS IN CASE OF POST-MYOCARDIAL-INFARCTION SYNDROME

Erythrocyte-sensitising extract	Inhibiting extract		
	Human heart	Human and Rabbit kidney	Other mammalian heart
Human heart	+	0	±
Dog heart	+	0	±

+ signifies complete, ± partial, inhibition of hæmagglutination

The concept [19] of autoantibodies as a cause of disease is not supported by our finding circulating anti-heart antibodies in rabbits without any pathological change in the heart Probably these autoantibodies are a consequence rather than a cause of tissue destruction The pathogenic autoimmune reaction may be due to the action of cell-bound antibodies [20] or "forbidden clones" as suggested by Burnet.[21] Be that as it may, the presence of circulating organ antibodies may be assumed to indicate autoimmune disease

A striking finding in the present experiments was the similarity in the anti-heart antibodies produced by immunised rabbits and by the patient with post-myocardial-infarction syndrome This seems to support Dressler's suggestion [14] that the syndrome is due to an autoimmune reaction, though the initiating stimulus here is different from that in the experimental animals

The low hæmagglutinating titres found in other positive human sera prevented characterisation of the antibodies, but they may be identical with those described by Dornbusch [4] Absence or low titre of antibody may be attributed either to adsorption of antibody on heart tissue or to inability to react to this specific antigen

Thanks are due to Prof A Laufer for the histological examinations and to Dr D Nelken for his helpful advice The experimental work in this communication forms part of the subject of the PH D thesis of one of us (I G.)

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ADDENDUM

We have since found three further cases with high titres of specific heart autoantibodies similar to those found in the case of post-myocardial-infarction syndrome Two of the cases suffered recent myocardial infarction and the third had recently undergone mitral valvotomy

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" Among the professions, your best opportunity, money-wise, is to be a doctor In fact when it comes to money, it is better to be an independent physician than just almost anybody General practitioners on the average net around $16,000 a year, surgeons average about $35,000 (Psychiatrists average only $17,000, perhaps because their patients individually take up more of their time than ordinary patients) Most specialists average several thousand more Why have medical practitioners succeeded in pulling so far ahead of other professionals ? A scarcity—an artificial one, some charge—has been created In 1900, there was one licensed doctor for every 578 people By 1940 the proportion of doctors had shrunk to the point where there was one for every 750 patients, or, if you consider only those still in active practice, there was one active doctor for every 935 persons '—VANCE PACKARD, *The Status Seekers*, p 99 London, 1960

Reviews of Books

Essential Principles of Pathology

JOHN W LANDELLS, M.B, M.R.C.P, reader in pathology in the University of London at The London Hospital London Pitman Medical Publishing Co 1959 Pp 278 25*s*

SOME will be tempted to dismiss this as a cram book, but they would be very wrong, for though it is cheap and could serve as efficiently as any cram book it is in fact an honest and well-thought-out attempt to produce a real introduction to pathology at a level which enables the slower undergraduate to read with profit Too often "introductions" to pathology deal almost exclusively with principles, disregarding the fact that basic principles can be terribly hard things to grasp *first*, and that in subjects like pathology it is often best to build foundations after the ground floor Judging fairly accurately the capacity of the average student, Dr Landells has not included all the things he thinks ought to be learnt, but as many as he thinks will in practice be learnt.

Standard textbooks of pathology have been written by men who in their time were outstandingly intelligent undergraduates, and, good though some of the available examples are, many textbooks seem to be concerned less with helping the student with pathology as a subject he meets in his course and more with serving him as a reference text for the rest of his life They aim to be accurate, judicious, and, above all, to leave nothing out too often it is the criticism of fellow pathologists that the author fears, rather than that of more junior readers For the bright student who is best on a tough diet, they are excellent, but they are heavy going for the average, and often nearly unintelligible to the tail end. Dr Landells seems to be attempting to reproduce the kind of teaching, simplified when it can be honestly simplified, that a conscientious teacher well in touch with his audience tries to give when early flourishes are over and examinations loom His 270 uncrowded pages cover most of what can be expected certainly few examiners could fail a student who was thoroughly familiar with this book. One difficulty is that no two pathologists would agree as to what are the *essential* facts of pathology, and in an attempt to retain the immediacy of verbal teaching Dr Landells occasionally lapses into sentences that will irritate some readers A few of his classificatory passages are of questionable logic. But this is a book that sets itself a worthwhile though smallish target, and hits it fairly Undergraduates who have no hankering after distinctions should welcome it.

Antibiotic Therapy for Staphylococcal Diseases

Editors HENRY WELCH, PH D, editor of *Antibiotics and Chemotherapy*, Washington, D C, MAXWELL FINLAND, M.D, associate professor of medicine, Harvard Medical School New York Medical Encyclopedia, Inc. London Interscience Publishers 1959 Pp 208 34*s*

ANTIBIOTIC-RESISTANT staphylococcal infections have now reached formidable proportions, they complicate operations, contaminate hospital nurseries, and exalt the virulence of influenza epidemics Staphylococci spread on the skin, persist in the nose, and circulate in the blood, whence they may settle with disastrous effect in brain and bone Their disregard of antibiotics has placed all those concerned, from pædiatrician to geriatrician, in a position of growing anxiety against mounting morbidity and mortality Various steps to reduce the hazard include vigilance against cross-infection, combinations of antibiotics, rotation of drugs, measures to improve host resistance, and, fortunately, some new antistaphylococcal agents

This authoritative monograph gives a critical account of the problem and evaluates the six latest antibiotics to join the fray—erythromycin, oleandomycin, novobiocin vancomycin, ristocetin, and kanamycin The six chapters describing them are the most modern and comprehensive accounts available In an opening chapter, Dr Welch outlines the development of the staphylococcal menace and the impact of earlier antibiotics upon it And finally Dr Maxwell Finland compares the relative value of the various antistaphylococcal drugs and provides a perspective for those who are bewildered as well as bedevilled by the staphylococcus

Statistical Methods in Biology

NORMAN T J BAILEY, D SC., reader in biometry, University of Oxford London English Universities Press 1959 Pp 200 25*s*

THIS short book provides a clear account of the principles underlying the standard statistical methods and the steps required for the calculations Using a minimum of mathematics, Dr Bailey illustrates the techniques with examples from various fields of biology and medicine The topics covered are orthodox (occasionally, even, old-fashioned), but two valuable innovations are introduced. There is an excellent chapter on computing and on the use of desk calculating machines, and a final section of the book, on green paper, contains a glossary, some necessary tables, and a 26-page summary of the methods described earlier This is one of the best books of its type

Recent Advances in Public Health

2nd ed J L BURN, M D, D.HYG, D P H., medical officer of health, City of Salford London J & A Churchill 1959 Pp 370 40s

THIS book has been entirely rewritten, and it is misleading to call it a second edition, twelve years after the first, when its function is to tell about recent advances It does so in a very pleasant style, and, in addition to the usual references, there are suggestions about books and published papers for further reading, and a most useful list of voluntary organisations willing to help Dr Burn has intentionally restricted the scope of his book to give a more detailed account of the advances on a narrower front, the practical day-to-day working of some of the public-health services at local level in Britain. The balance between the individual, the community, and the environment has come down heavily with emphasis upon the personal services, personal relationships, and clinical involvement. No doubt that truly reflects the preoccupations of the National Health Service in its first ten years Some of the advances have taken the public-health services deep into the therapeutic spheres of the hospitals and general practitioners, usually by that happy multiprofessional cooperation which runs as a theme of hope throughout the book. It may be hard for the public-health service to find the time, or be able, to untangle itself to meet the wider challenge of modifying man's environment to meet the needs of man. Ionising radiations just throw their shadow across only a corner of the text

This is a book for the public-health practitioner rather than the student, as any evaluation of advance must be. It demands some established experience to keep the sophisticated minutiæ of British personal services in perspective with the greater epidemiological and environmental changes in the world today, and to see that there is ample scope for advance on a broader front, with perhaps good hope of a breakthrough before the next edition. Dr Burn concludes with a timely reminder that the promotion of health is a bigger concept than the mere prevention of disease There is a lot in this book to turn to for refreshment and to think about.

The Archetypes and the Collective Unconscious

C G JUNG The collected works vol 9, part 1 Editors SIR HERBERT READ, MICHAEL FORDHAM, M.D, GERHARD ADLER, PH.D Translated by R. F C HULL London Routledge & Kegan Paul 1959 Pp 462 52*s* 6*d*

THIS large and beautifully produced volume is rich in format and in content, and brings together writings of Professor Jung formerly published in journals and books The text consists of six sections the first includes papers on archetypes of the collective unconscious and the concept of the collective unconscious, section 2 deals with psychological aspects of the mother archetype, section 3 is concerned with rebirth, section 4 with the psychology of the child archetype and the psychological aspects of the Kore, section 5 is on the phenomenology of the spirit in fairy tales and the psychology of the trickster-figure, and section 6 contains chapters on conscious, unconscious, and individuation, and a study in the process of individuation There are 80 plates, 29 in colour, and 5 figures

Anyone familiar with Jung's ideas will be delighted with this book, while to the sceptic or the novice the chapter in section 1, on the concept of the collective unconscious, may be recommended as an introduction (appropriately enough, it is the text of a lecture given to the Abernethian Society at St Bartholomew's Hospital)

The Golden Age of Quackery

STEWART H HOLBROOK London and New York The Macmillan Company of New York 1959 Pp 302 34s 6d

EIGHTY years ago the United States was expanding at a rate greater than that of any nation in the history of the world Its population was increasing by more than a million a year, and, numerically and geographically, much of that population had outstripped its supply of doctors Many of its inhabitants were comparatively wealthy, but ill educated (In 1870, the head of Harvard Medical School was reported as saying that "written examinations could not be given because most of the students could not write well enough") This was the *Golden Age of Quackery* of Mr Holbrook's title, the heyday of the patent-medicine maker

Unhampered by any licensing or narcotic laws it was possible at this time for unscrupulous manufacturers to sell "tonics" which derived most of their effect from being 50% alcohol, to compound "cures for the liquor habit" which owed their efficacy to a heavy dose of morphia, and to brew "cough syrups", each bottle of which contained a lethal dose of opium Stimulated by widespread and sustained advertising, the demand for such preparations could be raised to the point when it was difficult (even, in one case, for an organisation employing a thousand people) to meet it Nor was the market for these medicines restricted to the ignorant or the unlettered In 1861 the commissariat of the Union Army bought Hostetter's Bitters, the "Anti-Bilious Alterative" by the car-load The most notable feature of this nostrum was its 47% alcohol content, and a Civil War historian was later to write that "its vaunted remedial properties were sadly lacking but many a frightened Yankee at Gettysburg knew he faced Pickett's Charge as bravely as he did because of the swig of Hostetter's under his belt"

This book, by a distinguished authority on several aspects of American life at this time, gives an unusual and amusing account of these bogus remedies, of the picturesque medicine shows, the anatomical museums, and a host of devices calculated to assist in the task of parting the gullible from their money The Golden Age ended abruptly on Jan 1, 1907, when the Federal Pure Food and Drug Act became law And let any reader on this side of the Atlantic, who is inclined to smile at the credulity of his American cousins, reflect that comparable legislation in this country was delayed until 1941

Tools of Biological Research (Oxford Blackwell Scientific Publications 1959 Pp 183 37s 6d)—Edited by Mr H J B Atkins, this book records the proceedings of the successful symposium held at Guy's Hospital in October, 1958[1]

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[1] See *Lancet*, 1958, ii, 856

New Inventions

A TREPHINE NEEDLE FOR VERTEBRAL BODY BIOPSY

A MODIFIED trephine needle has been devised to overcome the defects of the method of aspiration biopsy described by Valls et al[1] With this method only small quantities of material can be obtained for examination, and in sclerotic lesions the needle cannot penetrate the cortex of the bone

With the new instrument larger samples can be taken from any type of vertebral lesion without injury to the patient

The needle has four parts (fig 1)

The needle holder (A) is a steel rule, boldly marked in centimetres, with a needle holder at one end fixed at an angle of 55° to the horizontal A sliding pointer makes it possible to adjust the distance from the mid-line at which the needle enters

The biopsy needle (B) is 16 cm in length and 3 mm in diameter and is marked in centimetres It has sharp cutting teeth at the distal end, and a milled circular head to facilitate gripping when the cortex of the bone is trephined

The exploring needle (C), which is 17 cm in length and 2 mm in diameter, is headless to permit the biopsy needle to slide over it when correctly placed

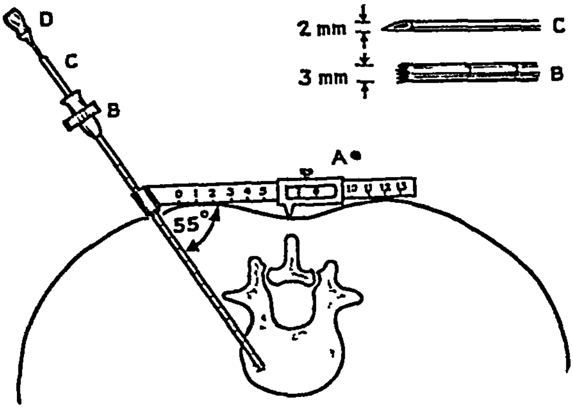
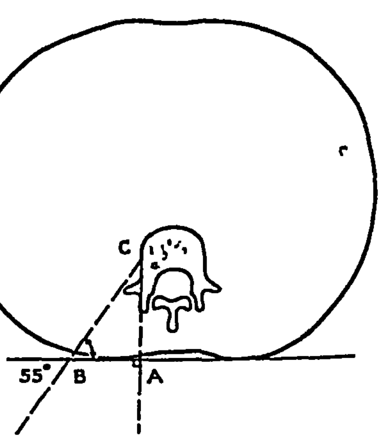


Fig 1

The infiltrating needle (D), which fits within the exploring needle, is used for infiltrating with local anæsthetic as the exploring needle is advanced It is withdrawn before the biopsy needle is inserted over the exploring needle



$$AB = \frac{AC}{\text{Tan } 55°} = \frac{AC}{1\ 43}$$

$$BC = \frac{AC}{\text{Sin } 55°} = \frac{AC}{0\ 82}$$

Fig 2

The position of the needle for biopsy is determined from a previous X-ray examination in which a steel rule has been included to allow for distortion The important factor is the point of entry, which must be some distance from the midline to avoid the transverse processes It may be calculated as suggested by Ray[2] the depth of the vertebral body is measured on the plate, and, as the needle is fixed at a known angle, the other measurements can be calculated trigonometrically (fig 2)

In practice, a piece of bone measuring 1 cm × 2 mm is obtained without difficulty this is large enough to show the trabecular pattern as well as to permit a wide field for examination of the cellular structure

This needle and several prototypes have been developed with the assistance of Mr J G Edwards, of the Edwards Surgical Company, 289, City Road, London, E C 1, and various members of the staff of the Orpington and Farnborough Hospitals, Kent, to whom I am greatly indebted

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[1] Valls, J, Ottolenghi, C E, Schajowicz, F *J Amer med Ass* 1948, 136, 376

[2] Ray R D *J Bone Jt Surg* 1953 35A 760

THE LANCET

LONDON 27 FEBRUARY 1960

The Unclaimed

Of the world's two and a half million unsettled refugees about a hundred thousand are on our doorstep, in Europe Some have been Stateless sojourners for fifteen years, leading a half-life without home or work or hope, and a new generation is growing up which has known no other way Many organisations and workers are striving to end their plight, and, if what they have done falls short of the need, it is largely because they have been denied the means of doing more This is not necessarily due to imperviousness the opening of doors to Hungarians who left their country in 1956 showed that, when the imagination is fired, people will respond, and the success in some countries of appeals in the World Refugee Year betokens growing uneasiness about those who remain in temporary refuge

One fact is clear the four European countries which have unsettled refugees in large numbers—Greece, Italy, Austria, and Germany—cannot provide satisfactorily for all of them Ungrudgingly these countries continue to give asylum to new refugees whose status under the United Nations mandate is established Italy, far from rich, with 2 million unemployed or under-employed and with some 400,000 of her own citizens from overseas accommodated in camps, yet shelters and feeds 5000 unsettled refugees and accepts new ones as they cross the border About 90% of these emigrate, but 10% remain and are an added charge on the country's resources If Italy and her neighbours are prepared to grant asylum, so should others be the responsibility is international

This international responsibility cannot be fulfilled so long as the present immigration laws are retained Designed to protect native populations, these laws are archaic, futile, and harsh Their archaicism is evident from their insistence on freedom from signs of pulmonary tuberculosis Their futility is reflected in the experience of the Hungarian exodus, when thousands were allowed to cross borders with scant regard to security or medical checks no country seems to have been endangered or put to great expense Their harshness is shown by acceptance under them of the young and the fit while their less able relatives are excluded. Such negative selection is not only inhumane but also unfair it is inhumane because it tends to split families, and it is unfair because it leaves the handicapped to the care of the overburdened first country of asylum An early objective should be to secure that would-be immigrants are not considered as individual units, and that no family is barred from immigration simply because it has one or more disabled members after all, no family need cost the second country of asylum anything if a breadwinner can support his relatives One or two countries, recognising this, have already gone some way towards amending their immigration laws

Relaxation of these laws will not by itself enable all the "hard core"—those who have been rejected for immigration under mass schemes—to settle in a second country But we should free our minds of any idea that these people will necessarily be a burden on the community impaired vision in one eye, loss of a kidney, an untreated hernia, a healed tuberculous lesion, a stiff knee—these barriers to immigration under mass schemes do not prevent useful work On the other hand, the "hard core" also includes some—such as "unaccompanied" mothers with children—who will less certainly be self-supporting In the survey which appears on p 481 of this issue we suggest that priority should be given to these, to the tuberculous, and to the ageing and elderly—those over 45, unacceptable under mass schemes, who are not always fit for the heavy work which is all that can be offered in some of the first countries of asylum But the aim, with other countries, should be no less than the acceptance of all refugees who wish to leave the Continent. And common sense tells us that this task should be undertaken at once, for an employable person who is unemployed—as many at present are—is a needless charge on the community, and the longer he remains unemployed the harder will he find it to resume work

Europe's "refugee problem" can be solved and solved quickly, but only if more money is forthcoming and if nations deliberately accept more of the handicapped The Office of the United Nations High Commissioner for Refugees has been making good use of relatively small sums subscribed by individual Governments, both for resettlement and for integration Of our own voluntary bodies, the non-denominational Adoption Committee for Aid to Displaced Persons is noteworthy as the first organisation to have applied substantial sums to the resettlement of those in unofficial German camps—who, as a group, are perhaps in greater need than any other In our review we suggest that on the Continent refugees might be better served if the dozen or so main voluntary agencies worked in closer union The same may be true of voluntary bodies in this country If in this World Refugee Year the many British organisations had launched a united appeal instead of raising funds on their own behalf and at the same time participating in the appeal by the central committee, the impact would undoubtedly have been greater Is it too late to take a leaf from the copybook of Norway, which has a single refugee organisation? With its small population of 3½ million, Norway has an unparalleled record for accepting handicapped refugees, and in this World Refugee Year £520,000 was raised in the first drive So far the per-caput contribution is highest in Norway, where it amounts to nearly 4*s* Norway is followed by Sweden, the Netherlands, and New Zealand The United Kingdom comes fifth, with about 10½*d* per head our original goal of £2 million has lately been reached, and the goal has now been set at £4 million

We look back on the Victorian era as one of contrast between riches and slum poverty We should not let our grandchildren recall mid-20th-century Europe as a place of general prosperity with small islands of destitute Stateless people whom no nation claimed If this is to be avoided the flame which burned briefly in 1956 must be rekindled and kept alight the acceptance of Hungarians in that year (though the motives may not always have been purely humanitarian) is the one example of almost unreserved international effort Settling Europe's refugees will give us heart and confidence for the vaster issue of the two million in the Middle East and Far East In this endeavour let us be informed by **Edmund Burke** "It is not, what a lawyer tells me I *may* do, but what humanity, reason, and justice, tell me I ought to do"

[*Contributions may be sent to the United Kingdom World Refugee Year Committee, 9, Grosvenor Crescent, London, S W 1*]

Peptic Ulcer in Town and Country

Methods of estimating the frequency of peptic ulcer all have serious limitations, and the overall and regional prevalence of this common condition remains unknown Mortality, clinical, and necropsy statistics are almost always made within selected hospital populations, and varying standards of examination and diagnostic criteria reduce their value Population surveys, though expensive and time-consuming, probably provide the best basis for estimation, but they are limited by the fact that the criteria for the diagnosis of ulcer are by no means precise Notable in the field of population surveys of ulcer frequency has been the work of C N **Pulvertaft**[1] in York As a sequel to the pioneer work done in that city by **Visick**[2] on the surgery of peptic ulcer, **Pulvertaft**, with the help of medical and surgical colleagues, has managed to collect all new peptic ulcers developing in the city of York and in the surrounding country districts of Easingwold, Flaxton, and Pocklington in the five years 1952–57 As the size of the total population at risk was known it was possible, probably for the first time, to estimate ulcer frequencies accurately in an unselected population—105,371 in the city of York and in 33,335 people in the country area Particularly stringent diagnostic criteria were observed throughout ulcers were judged to be present when they caused acute perforation or hæmorrhage, when they were found at necropsy, gastroscopy, or operation, or where they were convincingly demonstrated radiologically

In the five years 1132 ulcers were found, 823 in men and 309 in women. Diagnosis rested, in both sexes, on clinical grounds in 3 out of 4 patients and on hæmatemesis in 1 in 6 The proportion of women with acute perforation (7 8%) was appreciably less than in men (13 7%), possibly because duodenal ulcers, which perforated more often, were relatively less common in women Of the 823 ulcers demonstrated in men, 658 were duodenal, 126 gastric, and 31 antral, and 8 had combined gastric and duodenal ulcers Of the 309 ulcers in women, 204 were duodenal, 89 gastric, and 11 antral, and 5 had ulcers in both sites The mean annual incidence per 1000 population aged 15 years and over was, for duodenal ulcer, 2 15 in men and 0 62 in women, and, for gastric ulcer, 0 53 in men and 0 31 in women.

Age had an important bearing on incidence There seemed in men to be an equal liability for duodenal ulcer to develop at any age between 25 and 64, and the risk was appreciably less under 25 or over 65 Gastric ulcers, in contrast, developed more often in men between the ages of 45 and 64 Women began to have symptoms from duodenal ulceration most commonly between 35 and 44, and ulcer frequencies remained high in postmenopausal and elderly women Gastric ulcers increased in frequency in women with advancing years, occurring most commonly in the elderly and middle-aged The increased frequency of ulcer and ulcer complications at the time of the menopause was emphasised by **Clark**[3] The overall age-incidence of ulcer in both sexes was remarkably similar to that in the necropsy data of **Watkinson**[4 5]

The influence of social class on the incidence of gastric ulcer had previously been demonstrated by **Morris** and **Titmuss**[6] and by **Doll** and others,[7] both groups being unable to show any similar relation for duodenal ulcer In the York survey the occurrence of both types of ulcer seemed to be influenced by social and occupational factors Thus, duodenal ulcer in men increased from 2 08 per 1000 in professional and semiprofessional classes, to 2 26 in artisans, and to 3 13 in semiskilled and unskilled workers Differences were even more striking in gastric ulcer, which increased in these groups from 0 34 per 1000 in professional and semiprofessional classes to 0 92 per 1000 in unskilled or semiskilled artisans The decreased liability of agricultural workers to ulcer, reported by **Doll** et al ,[7] was not confirmed in the country district around York

Striking geographical differences in the frequency of peptic ulcer have been reported in several countries **Dogra**[8] found that ulcer arose more commonly in Southern than in Northern India, and **Konstam**[9] reported more ulcers in Southern than in Northern Nigeria In Europe similar regional differences were reported from Sweden,[10] Italy,[11] and Denmark[12] In England in 1944, **Morris** and **Titmuss**[6] demonstrated lower mortality-rates from ulcer in rural than in urban communities **Watkinson**,[4] by a forward-planned necropsy survey undertaken at selected hospitals in England and Scotland in 1956, found that duodenal ulcer was significantly more common and caused more deaths in northern than in southern cities—a difference more striking in men than in women, and for duodenal than for gastric ulcer

Despite the difficulties of comparing clinical estimates of ulcer frequency with material collected in other ways, **Pulvertaft**[1] felt able to draw a few limited analogies to illustrate that regional differences might appear. Thus, the frequency of acute perforation in duodenal ulcer in men in York appeared appreciably higher than in Glasgow[13] and Aberdeen[14] but no similar trend was noted in women. Gastric ulcers perforated more commonly in York in both sexes. When comparing his clinical ulcer frequency with the necropsy material collected by Watkinson[5] in Leeds between 1930 and 1949, Pulvertaft used for comparison the frequency of chronic active ulcers found incidentally at necropsy, since these subjects might well have had ulcer symptoms in life and their death was unconnected with their ulcers. On this basis the incidence of duodenal ulcer in York and in Leeds was surprisingly comparable, but gastric ulcer seemed appreciably less common in York—findings which confirm the regional necropsy survey made in 1956[4]. When the annual risk of developing duodenal ulcer was computed, it again appeared that men living in the city of York were more prone to ulcer than Londoners, the risk being 2·58 per 1000 in York[1] and 2·07 per 1000 in London[7]. The regional differences in ulcer frequency and natural history are at present unexplained.

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[1] Pulvertaft C N *Brit J prev Soc Med* 1959, 13 131

[2] Visick, A H *Lancet*, 1948, i, 505, 551

[3] Clark, D *Brit med J* 1953 i, 1254

[4] Watkinson, G *Schweiz Z allg Path* 1958, 21, 405

[5] Watkinson G *Gut* (in the press)

[6] Morris J N , Titmuss R M *Lancet*, 1944, ii, 841

[7] Doll R Jones, F A , Buckatzsch M *Spec Rep Ser med Res Coun, Lond* 1951, no 276

[8] Dogra, J R *Indian J med Res* 1940 28, 145

[9] Konstam, P G *Lancet*, 1954 ii 1039

[10] Bager, B *Acta chir scand* 1929 64 suppl 11

[11] Ginnanneschi, G *Med d Lavoro*, 1939, 29, 65

[12] Alsted G Peptic Ulcer in Denmark Copenhagen 1953 See *Lancet* 1953, ii, 444

When ulcer frequencies in town and country were compared by Pulvertaft[1] interesting differences emerged.

Thus, ulcers were significantly more common in townsmen than in countrymen: frequencies per 1000 population for duodenal ulcer were 2·40 and 1·42, and for gastric ulcer 0·62 and 0·27 respectively (the possibility that differences might have been due to varying age-distribution of the population was excluded). That the differences were in all probability real was further suggested by the fact that acute perforations occurred more commonly in town than in country in a ratio of 1·7 : 1. There was evidence that the differences observed were disappearing with increasing urbanisation of the rural areas, for duodenal ulcer was twice as common in town as in country in 1952 and only 1·3 times as common in 1956.

It was surprising that no statistically significant changes could be demonstrated in women: ulcers were only slightly more common in women living in town than in the country (duodenal ulcer 1·2 : 1, gastric ulcer 1·5 : 1). This disparity was not altered after appropriate correction for the age-distribution of the population at risk.

Variations in ulcer occurrence between town and country could not therefore be explained by differences in age-distribution or social class or by the allegedly increased tempo of town life. York is a quiet cathedral town with good living conditions and it is not highly industrialised. It was possible that the more ambitious ulcer-prone subject might have migrated from country to town, but this could not wholly explain the changes recorded. In an attempt to explain the variations, Pulvertaft[15] investigated the smoking and, to a limited extent, the dietary habits of his urban and rural populations. Ulcer subjects were compared with a matched control population attending for radiological examinations at York hospitals, subjects with dyspepsia or bronchial neoplasm being excluded. Doll et al[16] found that there were significantly fewer non-smokers amongst ulcer subjects than among matched control patients of both sexes, and that gastric ulcers healed more rapidly and completely in patients who had stopped smoking. The York survey confirmed that a higher proportion of ulcer subjects smoked than did control patients both in town (84·3% to 77·8%) and in country (81·6% to 77·7%). Differences observed were barely significant, however, and the proportions of smokers in town and country were almost identical, suggesting that varying smoking habits between town and country people could not explain the differences reported. Food habits proved even more difficult to investigate, but a simple preliminary survey based on the amount of sugar added to everyday beverages suggested that towndwellers consumed more sweet and sugary foods than did countrymen. It was also shown that ulcer subjects, both in town and country, ate more sweet food than did control subjects of similar sex and age. Whether this interesting observation has a bearing on ulcer causation in general or whether it might explain regional differences in ulcer occurrence is uncertain, but the subject is being further investigated in York and seems to open up a new path for research into this perplexing problem.

Annotations

ACROPARÆSTHESIÆ AND THE CARPAL-TUNNEL SYNDROME

Since compression of the median nerve in the carpal-tunnel was described by Brain, Wright, and Wilkinson[1] in 1947, light has been thrown upon its nature by observations on the association of this syndrome with pathological conditions, such as acromegaly[2] and myxœdema,[3] in which the connective tissues swell, and attention has recently been directed to its occurrence in pregnancy. In a paper in this issue Dr Marcia Wilkinson reports fourteen cases in which compression of the median nerve developed during pregnancy, and suggests that trauma, weight increase, and hormonal relaxation of the transverse carpal ligament may all play a part in its pathogenesis. Her further observation that half her patients also showed evidence of compression of one or more cervical nerve-roots is of interest for several reasons. Some, though not all, of these patients showed radiographic evidence of cervical spondylosis. It seems probable that in pregnancy the physiological changes responsible for precipitating the carpal-tunnel syndrome may also produce symptoms by disturbing the normal anatomical relations of the roots of the brachial plexus, and that pressure on the nerve-roots is likelier if there is pre-existing narrowing of the intervertebral discs and foramina in the neck. But the association of cervical spondylosis with the carpal-tunnel syndrome is not uncommon apart from pregnancy, and often provides a difficult diagnostic problem. Is this association merely fortuitous, and due to the fact that both disorders are common in middle age and later, or, as Russell[4] suggests, does a sensory nerve react as a whole to trauma so that a lesion in one situation makes it, as it were, irritable in another?

A further point which emerges from Dr Wilkinson's observations, and from Russell's view if it is soundly

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[13] Jamieson, R. A. *Brit. med. J.* 1955, ii, 222.
[14] Weir, R. D. Unpublished data.
[15] Pulvertaft, C. N. Proceedings of the World Congress of Gastroenterology. Baltimore, 1958.
[16] Doll, R., Jones, F. A., Pygott, F. *Lancet*, 1958, i, 657.

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[1] Brain, W. R., Wright, A. D., Wilkinson, M. *Lancet*, 1947, i, 277.
[2] Kellgren, J. H., Ball, J., Tutton, G. K. *Quart. J. Med.* 1952, 21, 405.
[3] Murray, I. P. C., Simpson, J. A. *Lancet*, 1958, i, 1360.
[4] Russell, W. R. *Med. Pr.* 1958, 240, 1151.

based, is the undesirability of regarding acroparæsthesiæ as a symptom of a lesion in one particular situation, and of treating this symptom as though it were a disease. Before either the carpal-tunnel syndrome or cervical spondylosis was discovered, acroparæsthesiæ were usually ascribed to some disorder at the thoracic inlet, and Walshe[5] included "acroparæsthesia" among the subtitles of an article entitled "nervous and vascular pressure syndromes of the thoracic inlet and cervico-axillary canal." He also thought that pregnancy played a part in producing acroparæsthesiæ in the thoracic-inlet syndrome.[6] Later the view that compression of the median nerve in the carpal tunnel was the main, if not the sole, cause of acroparæsthesiæ, gained ground, and the symptom then came to be regarded as an indication for surgical division of the transverse carpal ligament. But there is no doubt that the radicular symptoms of cervical spondylosis include acroparæsthesiæ, which, as in the carpal-tunnel syndrome, may come on during the night. By the time that wasting of the outer thenar muscles has developed, the diagnosis of median-nerve compression is easy, but when the symptoms are purely sensory it may be difficult, in the presence of cervical spondylosis, to decide whether acroparæsthesiæ involving the radial digits are due to median-nerve compression or to a lesion of the 6th and 7th cervical nerves, or possibly both. In such cases measurement of the conduction time in the distal part of the median nerve may be a valuable aid to diagnosis.

Acroparæsthesiæ, then, are no more a nosological entity than headache, but a symptom, which may indicate disturbed function of the sensory nerves supplying the hand at one of three points in their course—the intervertebral foramina, the costoclavicular region, or the carpal tunnel. Before rational treatment can be begun both the site and the nature of the lesion must be determined.

Dr Foster's paper in this issue, describing the improvement in the carpal-tunnel syndrome produced by injection of hydrocortisone, is further evidence of the part played by œdema in the production of symptoms. The high relapse-rate he reports suggests that his treatment was not removing the cause of the syndrome. Moreover, he was dealing with early cases—two-thirds of his patients showed no abnormal physical signs. It seems, therefore, that surgery is still the treatment of choice for those patients whose disorder is not naturally reversible, as in pregnancy, and has reached the stage of objective damage to the nerve.

SALMONELLÆ IN IMPORTED MEAT

MEAT and especially "meat products" are responsible for more salmonella infections in man than all other kinds of food together. This has been clear in every annual report on food-poisoning issued by the Public Health Laboratory Service, but the reason has been obscure. In this country salmonella infections rank low in importance among the diseases of the larger domestic animals. (Admittedly, many are never reported, but the notifications of human disease are likewise incomplete.) Few animals with obvious salmonella infections reach the slaughterhouse. Attempts by bacteriologists to detect inapparent infections in home-grown carcasses have given very varied results at different times and places, but in general it would be surprising if 1% of these were infected. A recent paper on the bacteriology of imported meat may help to explain this anomaly.[1] The material was of two kinds—chilled carcasses and frozen boneless beef, veal, and mutton. Of 304 samples of the former 3.1% contained *Salmonella* spp.; of 890 samples of the latter, 10.3%. If these figures are broken down into the countries of origin they are even more striking: 18% of samples of boneless veal from country A were found to be infected. From country B both boneless and carcass meat gave figures of 7.5%. Because some of these samples were very small, it would be unwise to read too much into the figures, but beyond doubt quite a lot of infected meat is coming into this country. Incidentally about the same proportion of samples harboured heat-resistant strains of *Clostridium welchii*: without comparable figures from other sources this may mean something—or nothing.

Fourteen species of salmonella were isolated. *S. typhi-murium* was the commonest, and the rest—including one strain of *S. paratyphi B*—represented a fair selection of the species which most often cause food-poisoning in western Europe. What is interesting is that, except for the ubiquitous *S. typhi-murium*, the species found in beef and veal were not those most often associated with bovine disease. *S. dublin*, by far the commonest cause of salmonella infection in cattle in this country, was never isolated. The species in carcass meat have all been found in living cattle (though rarely), but some of those in the boneless meat have never been found in cattle at all. We are admittedly very ignorant of the distribution of *Salmonella* spp. in Nature, but these findings almost suggest that the organisms in this meat were not derived from the living animals but from some extraneous source. None of the exotic species of salmonella recently detected in feeding-stuffs were isolated from this meat.

The authors of this paper are not in a position to tell us about the conditions of slaughter of these imported carcasses or the methods of preparing the boneless meat. Experience shows that one contaminated knife may spread infection far and wide in a butcher's shop. Until more is known of this, it would be idle to speculate upon possible sources of infection of the living animal. Information on this subject is hard to obtain at home, but some Continental countries take meat inspection more seriously than we do. It would be of great benefit if the veterinary profession were to make a really extensive survey of the infection of carcass meat with salmonellæ—say at six large abattoirs over at least two years.

The dangers of this infected meat are obvious, but we doubt whether a cut off the joint is a common source of human infection. As a nation we prefer our meat sterilised. The danger lies mostly in the use of infected meat for making sausages and such savoury delights. Few cooks do more than warm the outside of a sausage, and travellers say that in some backward parts of England sausages are eaten raw. It is astonishing, indeed, that infections are so few, but most of us are probably resistant to all but an astronomical dose of all salmonellæ except *S. typhi*. Protection must be through a change in the composition of sausages or in the national eating habits—and it is hard to guess which is the less likely. Plainly the importation of this infected meat should be prevented so far as possible. The Imported Meat Regulations (1937 and 1948) may or may not apply—a question that can probably be settled only in the courts. Sterilisation by gamma irradiation has been suggested as a remedy, and though this method is still in the stage of experiment it ought to be considered seriously Indeed the whole problem of imported salmonellæ—in meat, poultry eggs, and offals—has now reached a point when it deserves the attention of the Ministry of Health and the Board of Trade. Unfortunately, in spite of the enthusiasm of the bacteriologists, it is difficult to be sure whether more than a very few human infections are derived from these sources

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[5] Walshe, F. M. R. Modern Trends in Neurology (edited by A. Feiling) p. 512. London, 1951.

[6] Walshe, F. M. R. *Brit. med. J.* 1945, ii, 596.

[1] Hobbs, B. C., Wilson, J. G. *Mon. Bull. Minist. Hlth Lab. Serv.* 1959, 18, 198.

CLINICAL RADIOLOGY AND HÆMOPHILIC BONES

THE *Journal of the Faculty of Radiologists* has been renamed *Clinical Radiology*, and important changes have been made in its format. The policy of the editorial board remains "the publication of scientific papers of interest to diagnostic radiologists and to radiotherapeutists with the main emphasis on clinical radiology" But papers on experimental and similar work with clinical implications will be welcomed, and the first number[1] includes a paper on metabolism of radioactive materials in the human body by Prof W V Mayneord, and one on marrow transplantation after radiation by Dr K. A Porter It also includes a most interesting article on bone and joint changes in hæmophilia and Christmas disease, by Dr J H. Middlemiss, of Bristol, which is illustrated by many excellent and unusual radiographs

One of the commonest manifestations of hæmophilia is hæmarthroses The bleeding into a joint is often repeated, the same joint being involved on several occasions this causes damage to the structures in the joint and curious and characteristic lesions in the bones, especially in the epiphyses

The joints most usually affected are the knees, ankles, and elbows, hip-joints and shoulder-joints are less commonly involved. Repeated hæmarthroses can eventually cause much deformity and serious limitation of mobility, and they account for the presence of so many hæmophiliacs in homes for cripples. The synovial cartilage is slowly destroyed, so the joint space becomes steadily smaller, so-called cysts, sometimes multiple, appear subarticularly below the bone surface In children the intense periarticular hyperæmia associated with recurrent repair processes causes accelerated growth, and exceptionally large epiphyses may be formed. When the patient grows up unusually large bone ends may be formed in joints that have been involved in repeated hæmarthroses, and Dr Middlemiss has a striking radiograph showing how one femoral head has become larger than the other from this cause.

Illustrations show other ways in which radiology can help in hæmophilia. For example, intermittent small-bowel obstruction develops sometimes in hæmophilic children and a plain film of the abdomen shows such a case due to intussusception. A retroperitoneal hæmatoma in the right iliac fossa gives rise to symptoms and signs that closely mimic those of acute appendicitis Operations are still to be avoided whenever possible in hæmophilia, and Dr Middlemiss reproduces plates showing firstly the obliteration of normal landmarks on the right side of the abdomen with displacement of the bowel shadows to the left, and secondly an excretion urogram with the right ureter displaced medially by the retroperitoneal hæmatoma. In such a case laparotomy is unnecessary Another odd condition may be found (usually in the iliac bones) repeated subperiosteal hæmatomas cause atrophy of the underlying bone, and eventually a large area is destroyed some new bone may be formed in the hæmatoma mass This "pseudo-tumour" gives a very characteristic radiographic picture, which again is very well illustrated. This paper should be consulted by all interested in hæmophilia and in joint disease. It and its companions in the first issue of *Clinical Radiology* set a high standard.

CELLULAR ORIGIN OF RHEUMATOID FACTOR

THE great majority of patients with rheumatoid arthritis have in their plasma a factor capable of agglutinating diverse particles coated with γ-globulin.[1] Various refinements of the original test have increased its sensitivity, and a positive reaction is now obtained in nearly all patients with the disease. The site of origin of this factor, its relationship to a true antibody, and the nature of the γ-globulin with which it reacts are still somewhat obscure.

The origin of the rheumatoid factor has been fruitfully studied by Mellors and his colleagues,[2] who applied Coons' fluorescent-antibody method. It had already been established that human γ-globulin heated to 62°C for ten minutes reacted specifically with the rheumatoid factor[3] A histochemical reagent for detecting the factor was therefore prepared by the heat-aggregation of γ-globulin after it had been conjugated with fluorescein isothiocyanate. Sections of fresh frozen tissue treated with this reagent should, when viewed with ultraviolet light, show by an applegreen fluorescence the histological sites of distribution of the rheumatoid factor With this reagent tissues from 10 patients with rheumatoid arthritis were studied. A control group of 22 patients without rheumatoid arthritis included many with other forms of chronic arthritis such as traumatic and degenerative osteoarthritis and tuberculous synovitis The tissues studied included synovial membrane, lymph-nodes, subcutaneous nodules, skin and muscle. The results were quite unequivocal. The rheumatoid factor was found exclusively in the tissues of the rheumatoid patients and was identified in only two cell types—plasma cells and the reticulum cells of the germinal centres of some lymph follicles In the synovial membrane the positive cells constituted a small minority of the plasma cells present, while in the affected follicles all the reticulum cells were stained, but these follicles constituted only about 10% of those present. Positively stained plasma cells were also present in the affected lymph-nodes but were restricted almost entirely to the medullary cords

Since the rheumatoid factor belongs to the group of γ-globulins with a sedimentation coefficient of 19S, confirmation of the above results was sought by using a fluorescent rabbit antibody specific for this fraction of human serum. The cells stained by this reagent always included those stained by the fluorescent-aggregated γ-globulin. It was not confined to these, of course, because not all 19S globulins have the specificity of rheumatoid factor

The results do not prove that the rheumatoid factor is an antibody True, the factor is apparently formed by cells now widely accepted as responsible for the synthesis of circulating antibody, but, as Mellors points out, these cells can synthesise non-antibody protein—for example, in multiple myelomas Nevertheless the distribution of the factor is exactly what would be expected were it indeed an antibody

As regards the nature of the γ-globulin with which the factor reacts it is difficult at present to decide between two hypotheses the first accepts the reactant as normal γ-globulin with a sedimentation coefficient of 7S,[4] and there is convincing evidence that in vivo the rheumatoid factor exists as a complex between several molecules of 7S globulin and a molecule of 19S globulin On this view the precipitation of the factor with aggregates of 7S globulin is due entirely to the more ready precipitability of the large molecular aggregates According to the second hypothesis the aggregation of the reactant molecules is of secondary importance, the primary necessity for the reaction being some change in shape of the molecules brought about by heat or by their adsorption on to various surfaces[5] Unless there is some change of this sort, it is difficult to understand why, for example, the 19S rheumatoid factor should exchange its associated normal 7S globulins for those on a latex particle or a sensitised red blood-cell

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[1] *Clin. Radiol.* [illegible] 1960 11 no 1 Published by Messrs E & S Livingstone Edinburgh and London Subscription £3 3s per annum (four issues)

[1] Ziff M *J chron Dis* 1957 5, 644

[2] Mellors R C, Heimer, R, Corcos J Korngold L *J exp Med* 1959 110 875

[3] Christian C. L. *ibid* 1958 108, 139

GOODBYE TO "METABOLIC INSUFFICIENCY"

THE syndrome of "metabolic insufficiency" or "non-myxœdematous hypometabolism"[6] has been defined[7–11] as a condition in which such symptoms as fatigue, weakness, and nervousness are associated with a low basal metabolic rate, normal serum-protein-bound iodine, and normal uptake of radio-iodine by the thyroid gland Patients with this syndrome are said to respond well to triiodothyronine, but not to thyroxine or thyroid extract, and a peripheral defect in ability to respond to thyroxine has been postulated We have previously expressed scepticism about the existence of this syndrome,[6] together with some concern at the possibilities its supposed existence offers for commercial exploitation We suggested that the crucial issue was whether these patients really responded to triiodothyronine but not to thyroxine, and that the only satisfactory way of deciding this was by a properly conducted "double-blind" trial

This suggestion has now been acted on by M E Levin,[12] of St Louis, Missouri 22 patients were identified by the criteria listed above (these were all that could be found in a year's study of 2290 medical outpatients) Detailed studies were made on 6 patients with the syndrome Each received thyroxine (0 3 mg daily), or triiodothyronine (0 075 mg daily), or an equivalent number of lactose tablets, in random sequence for periods of a month All tablets appeared identical, and the investigator did not know which medication the patient was receiving The final statistical analysis showed no significant differences in the frequency with which symptoms were relieved by the three types of tablet

In this group of patients neither thyroid hormone caused any greater subjective improvement than lactose tablets, and triiodothyronine was in no way superior to an equivalent dose of thyroxine The symptoms therefore cannot be attributed to any form of hypothyroidism, or to irresponsiveness to thyroxine Since Levin also showed by psychometric tests that these patients had abnormal personality patterns, it seems likely that their symptoms were essentially psychogenic This careful trial provides the first objective evidence about "metabolic insufficiency" Since the results were entirely negative it reinforces the doubts we previously entertained about the existence of this syndrome We hope that "metabolic insufficiency" will quietly disappear from medical literature.

INSTITUTIONAL POPULATIONS

OUR institutions serve a variety of purposes, and the people in them are a mixed company with little in common save that they have all been deprived of something—children of the care and support of their parents, old people of the strength and activity which gave them independence, patients of mental or physical health, and prisoners of their liberty Though institutions are an essential part of our social service we are beginning to realise that they should be used sparingly Wherever possible, children should be found foster families, old people should be supported in their own homes, mental patients should be looked after in the community, young delinquents should be put on probation On the other hand practical difficulties—small families, cramped housing, women with jobs, complex medical procedures—balance this theoretical shift of social care from the institution to the community, and information about the use that is in fact being made of our institutions today would be a helpful guide to planning the social services of tomorrow Dr Brian Abel-Smith and Mr Robert Pinker[1] offer some pointers about this in their comparison of institutional populations in 1911 and 1951

Though changes in administrative procedure and in official classifications naturally preclude an exact comparison, they have been able to reach some broad conclusions which are of interest They have divided institutional populations into the physically ill, the mentally ill, welfare cases, and lawbreakers Between 1911 and 1951 the physically ill appear to have increased by 21% and the mentally ill by 26% more than would be expected from demographic changes alone, which suggests that despite the expanding domiciliary services there has been no decline in the proportion of people looked after in hospitals On the other hand the proportion of the population looked after in welfare institutions (in which they include homes for children, cripples, blind, deaf and dumb, epileptics, and the aged and infirm) fell by nearly 51% The confinement of lawbreakers increased by 36%

Analysis of the figures according to sex, age, and civil state was also complicated by changes in procedure and terminology But there has been a clear decline in the age of offenders Again, among the mentally ill the proportion of single people in institutions doubled between 1911 and 1951 for both sexes The increase was greatest among those under 45, but this may be partly due to people in the workhouses of 1911 who would today be classified as mental defectives The proportion of people over 65, making a similar allowance for the workhouse population, decreased between 1911 and 1951 Among the welfare cases there seems to have been unhappily a considerable increase in the proportion of children and an unexpected but welcome decrease in the proportion of the aged, particularly men, in institutional care

Dr Abel-Smith and Mr Pinker emphasise that their study makes no claim to measure social needs or physical or mental morbidity, but they believe that at the very least their conclusions "do not support theories of increasing family neglect or of a trend towards 'medicated survival'"

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[4] Edelman, G M, Kunkel, H G, Franklin, E C *ibid* p 105

[5] Glynn L E, Holborow E J, Johnson G D *Proc R Soc Med* 1957, 50, 469

[6] See *Lancet*, 1956 ii 826 *ibid* 1957, ii, 992

[7] Freedberg A S, Kurland, G S, Hamolsky, M W *New Engl J Med* 1955 253, 57

[8] Kurland G S, Hamolsky M W, Freedberg A S *J clin Endocrin* 1955 15 1354

[9] Tittle C R *J Amer med Ass* 1956, 162 271

[10] Fields E M *ibid* 1957, 163, 817

[11] Morton J H *ibid* 1957, 165 124

[12] Levin M E *J clin Endocrin* 1960 20 106

[1] *In a paper to the Manchester Statistical Society on Feb 10 1960*

EUROPE'S REFUGEES IN 1960

A Lancet Survey

The World Refugee Year was launched last June in accordance with a resolution by the General Assembly of the United Nations, which named the aims as (1) to encourage interest in refugees and to secure additional financial contributions, and (2) to provide additional opportunities for permanent solutions, through voluntary repatriation, resettlement, or integration In the United Kingdom a central committee was set up, with the following objectives to aid the 160,000 unsettled refugees in Europe who came under the mandate of the United Nations High Commissioner for Refugees, to promote settlement of the 8000 European refugees on the mainland of China, to aid the Chinese refugees, numbering close on a million, in Hong Kong, and to aid the million refugees (nearly all Arabs) from Palestine

This account of refugees in Europe is based on the observations and inquiries of a member of our staff in Italy, Austria, and Germany

THE BACKGROUND

It is all too easy to think and speak of refugees either, on the one hand, as units to be added to a statistical table or, on the other hand, in terms of emotional anecdote In fact the refugee is an ordinary person in an extraordinary position his need, like that of the next-door neighbour in trouble with his bank overdraft, is for informed and dispassionate advice and well-directed help Each new refugee is an emergency, for the longer he is denied a full productive place in society, the harder will it be for him to take such a place—and incidentally the heavier will be the charge on those who sustain him in unwilling idleness

In Europe, as elsewhere, the refugee situation is never static a refugee may return to his own country, settle where he has first sought asylum, emigrate, or even move illegally to a second country where he believes the prospects to be brighter And all the time some countries—notably Italy and Austria—are receiving new refugees Consequently, no estimate of numbers is ever up to date

Last autumn, according to the office of the United Nations High Commissioner for Refugees (U N H C R.),[1] Germany, Austria, Italy, Greece, and France had 110,000 refugees (including 22,000 in camps), compared with 160,000 (including 40,000 in camps) a year earlier, and this reduction was achieved despite an influx of 6000 new refugees during the year

These totals, however, include only those who satisfy the exacting U N definition of a refugee—namely, one who has been driven from his country by political or other persecution or by fear of such persecution. The definition excludes the migrant who belongs ethnically to the country in which he seeks asylum (such as Pakistanis and Indians who were the victims of a new demarcation line, and the Vietnamese and Koreans who moved to the south of their countries during and after wars) It also excludes " economic " refugees who migrate in search of work. Thus the total of unsettled immigrants in Europe is far greater than 110,000, those who do not fall within the U N H C.R.'s definition are in danger of being returned to their own country, and are anyhow at a material disadvantage.

Owing to differences in the interpretation of " refugee " and the narrow U N H C R definition, the totals shown by the Government, by U N H C R, and by the Intergovernmental Committee for European Migration (I C.E.M)[2] are widely discrepant

The immediate help and the eventual solutions offered to the refugee differ distinctly between one country and another Whether the refugee is encouraged to stay or to move on depends partly on the economy of the recipient country Thus neither Greece (where refugees are relatively few) nor Italy (where they are much more numerous) is interested in refugees as a source of labour Indeed, Italy has 2 million unemployed or underemployed of her own and no fewer than 400,000 of her citizens in camps up and down the country [3], and a steady stream of Italians moves out of the country to more prosperous areas, including the German Federal Republic. Germany, by contrast, with her bustling economy has an economic interest in retaining all who are fit to work (Likewise, she is politically interested in retaining the 12 million of her nationals from East Germany as a lever in her efforts to secure reunification These 12 million do not rank as refugees under the U N.H C R 's definition) Austria occupies a middle position Though her unemployment figure is fairly high, especially in winter, she may wish to add to her labour force in order to hasten industrialisation of the relatively undeveloped eastern region, but she is anxious not to swamp her own small population of $7^1/_2$ million with foreign nationals

Such considerations, however, are certainly not in the foreground in Italy and Austria, which, at great cost to themselves, have (like Germany) steadfastly kept the door open to all proved refugees and have, it may be thought, treated the " economic " refugees not ungenerously

A recent brief visit to Italy, Austria, and Germany left three main impressions first, that refugees should be accepted as an international responsibility, the cost at present falling far too heavily on a few countries, secondly, that with effort and good will the tragic situation of the " old " refugees [4] can be transformed, and thirdly, that the machinery for dealing with refugees, which has been built up piecemeal over the years, is unworthy either of those who operate it or of those for whom it is operated.

The following account is devoted chiefly to Austria because (though the numbers are admittedly smaller than in Germany) great progress has been made towards securing integration or emigration for all, and because the emphasis is not mainly on emigration (as in Italy) or mainly on integration (as in Germany) but on both together

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[1] The office of the U N.H C R, the successor of the International Refugee Organisation, is financed by direct contributions from Governments Its main concerns are to protect the interests of refugees falling within the U N H C R definition, and to help to provide for their settlement or emigration, but U N H C R. is itself non-operational

[2] I C E M was created in Brussels in December, 1951, to help to restore the equilibrium between the overpopulated and the underpopulated nations through orderly migration of Europeans who could not emigrate without international assistance Under its aegis nearly a million emigrants (45% of them refugees) have left Europe I C E M has close ties with, but is distinct from, the United Nations At present 29 countries are members Strangely the United Kingdom is not a member—a defect which it is believed will soon be repaired

[3] These Italians are from the former Italian islands in Greece, from Egypt, from Tunis, from former Italian colonies, and from territory ceded to Yugoslavia

[4] ' Old ' in this context denotes, in the case of Hungarians, those who sought asylum before Oct 23, 1956, and, in the case of other nationals, those who sought asylum before the beginning of 1956

AUSTRIA

NEW REFUGEES

About 300 people a month cross the border illegally from Yugoslavia

Each is interviewed by the police, who decide whether he shall be graded as a political refugee The decision is conveyed to the representative in Austria of the U N H C R , who may make representations on the decision If no agreement is reached, a joint meeting is held, but naturally the final decision rests with the Austrian Government

Since last September those seeking asylum have been sent to a central reception centre in Traiskirchen, where their applications are investigated Only a very few are returned to the border all others either remain in Austria or seek to emigrate

On entry to the country the refugee registers with I C E M and a voluntary agency,[5] to which he looks for counsel and help in arranging emigration or settlement, for supplementary food and clothes and money, and for moral support If he wants to settle in Austria he may seek grants from his agency, U N H C R , and the United States Escapee Programme (U S E P),[6] and apply to the *Arbeitsamt* for work If he wishes to emigrate he may have to wait for two years

Of the "*new*" *Yugoslavs* (i e , those who have entered Austria since the end of 1955) the majority (rather over 60%) are single men aged 18–40, about 15% are single women, 12% family units, 6% childless couples, 2% over the age of 60, and 0 5% unaccompanied youths under the age of 18 Of the 2100 unsettled Yugoslavs in the country in January, all but 100 had declared that they wished to emigrate

There is an interesting contrast between these "new" Yugoslavs and the remaining "*new*" *Hungarians* (i e , thos who entered Austria in 1956) Of this second group famil units account for over 40%, single men for 25%, childles couples for 20%, single women for 10%, and unaccompanie youths or elderly people for the rest Moreover, of the 10,00 remaining unsettled Hungarians, no fewer than 7000 say tha they want to stay in Austria Many of these could hav emigrated, but they chose to remain, partly perhaps becaus they feel at home in Austria, which was formerly linked wit their country in the Austro-Hungarian Empire, but mostl because they believe that here better than elsewhere they ca keep in touch with relatives across the border

NEW AND OLD

The task of establishing the number and whereabouts of all refugees in the country is enough to make a statistician blench

On Jan 1 of this year there were 56,526 refugees in Austria under the U N H C R mandate Of this total, 6442 were living in camps and institutions under the federal administration, and 1186 were accommodated in homes or institutions owned by the various voluntary agencies, 1267 were in unofficial camps The remainder (47,631) were living in private accommodation, and, of these, about 17,000 were unsettled In addition there are about 270,000 one-time refugees who have taken Austrian nationality, including 10,000 living in camps administered by the federal authorities These people belong to one of eleven or twelve nationalities, with Yugoslav and Hungarian predominating 26,000 have registered with I C E M

ARRANGEMENTS BY GOVERNMENT, U N H C R , AND AGENCIES

Accommodation

The 137 unofficial camps contain only "old" refugees (40% ethnic Germans or Austrians and 60% foreign-speaking) These camps, of which some are privately owned, some belong to local authorities, and some are accidental aggregations, are (judging by the few seen) mostly pathetic shambles—dilapidated wooden shacks without semblance of satisfying primitive requirements The 42 official camps, run by the Government, are better often wooden Army huts, weatherproof and with more or less reasonable sanitation, but without protection from

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[5] Some of these agencies are religious and others are "national" organisations ("national" here meaning of the refugees' nationalities) The national agencies seem likely to dwindle or disappear This is perhaps regrettable as a refugee may be dealt with more understandingly by one of his own nationality On the other hand, some of the national agencies are not interested in securing integration, even though this may seem the most suitable solution All agencies draw by far the greater part of their funds from voluntary contributions, but U N H C R subscribes to the cost of their social workers and counsellors Shortage of such workers is seriously impeding the work of most agencies

[6] U S E P was established in 1952 to aid in the reception, care and maintenance, and resettlement of escapees from the Iron Curtain area of Europe and Asia This assistance, provided through voluntary agencies working under contract, is supplementary to that offered by international organisations The programme is administered by the Office of Refugee and Migration Affairs, Department of State

the noise of children next door or from the unwelcome visitor who calls at the front door which is also the bedroom door.

The Government aims to close all official camps by the end of 1962, rehousing those who do not emigrate in flats—which in some cases are being built on the site of the camp. 4000 flats are going up under a joint U.N.H.C.R. and Government scheme, each contributing, on average, 50% of the cost. These flats are excellent—spacious and well found. But the provision of a new home does not in itself solve any problem. A family which for years has been accustomed to the "security" of camp life needs strenuous preparation for the responsibilities of a home, and, having moved in, it will still need wise counselling, especially as there is little enough money for the unexpectedly heavy expenses unless the family includes a breadwinner.

This is not the fault of the Austrian Government which, with singular openhandedness, treats all refugees, with regard to financial and social benefits, as if they were Austrian citizens.

Under the social welfare scheme an unemployed single man receives 360 Austrian shillings a month (there are about 72 Austrian shillings to the pound sterling). A married man receives 560 Austrian shillings, plus 180 shillings for each child, per month. In official camps an unemployed man pays nothing. An employed man pays 35 Austrian shillings a month for rent and 8–9 shillings a day for food. In a flat he pays likewise 35 shillings a month, and the difference between this and the 100 shillings which is the economic rent is contributed by the Government. Because the U.N.H.C.R. contribution to the building cost is interest-free, the economic rent is somewhat lower than it would ordinarily be. Moreover, experience and standardisation are enabling the authorities to erect four flats for the cost of three earlier ones.

The restricted U.N. definition of "refugee" has given rise to difficulty. The Austrian Government relaxed its naturalisation laws to enable some ethnic Austrians to become nationals of the country. These people then automatically lost the chance of obtaining a flat under the joint U.N.H.C.R.-Government scheme. Accordingly, the Government has instituted a parallel scheme to build flats wholly at its own expense, but this is grinding to a halt for lack of money. Political pressure against this scheme is strong, as these "new" Austrians are commonly still regarded as foreigners who should receive no preferential treatment. They seem to have had the worst of both worlds.

Medical Care and Health

Hospital and other medical care is provided by the Government for refugees, in or out of camps, on the same terms as for Austrian citizens. The Government has set up a special home for unmarried mothers and their children.

A special sanatorium—which has a high reputation—exists for refugees, but fewer than 30 active cases of pulmonary tuberculosis are known to the authorities. In 1957 I.C.E.M. X-rayed on 70 x 70 mm. film the 18,000 remaining Hungarians, and found active or arrested tuberculosis in about 2.5%. Positive findings were reported to the local chest clinic and to the Ministry of the Interior. In 1958 I.C.E.M. initiated a similar survey of "new" Yugoslavs. Unfortunately this survey was terminated owing to lack of funds, but in the 400-500 cases examined the rate was again about 2.5%.

Disorders that seem to be especially prevalent include "weakness of the heart" (in most cases the symptoms are those of effort syndrome), hypertension, dyspepsia (possibly occasioned in some by unfamiliar food), and rheumatism.

EMIGRATION

Both Canada and Australia have in Austria permanent missions which select healthy and socially acceptable individuals and families for emigration under mass schemes. The age-limit is 45, or exceptionally 50 when family units are being selected. Close on 6000 emigrated in this way last year.[7]

At present, of I.C.E.M.'s case-load of 26,000, some 10,000–12,000 have declared that they want to emigrate, but any such estimate is bound to be inaccurate because a person who has been rejected again and again for emigration under mass schemes (as many have) tends to despair and not to bother to declare his wish to leave the country. Experience has repeatedly shown that many who have previously expressed no interest in emigrating seize on a firm offer when this is made under a special scheme.

The medical criteria for selection under mass schemes are confidential, and neither the refugee nor I.C.E.M. is officially informed of the reason for rejection. Thus a refugee may spend a year or longer presenting himself to one mission after another, and, having failed with all, still be in the dark as to the cause of his failure.

Although the criteria are not published, some of those rejected could clearly be brought up to the required standard by fairly simple measures—perhaps a hernia operation or even just the provision of spectacles. It is thus most important that each would-be emigrant should have at his disposal the advice of doctors who know roughly the missions' requirements and how they can be met, and who can inform those who have no hope of meeting these requirements: there can surely be nothing more demoralising than to move from mission to mission, each time being denied for reasons untold.

This need is well exemplified by suspected tuberculosis. The doctor examining for mass emigration usually has at his command a single chest radiograph (tomography is occasionally arranged). Sometimes the doctor defers a candidate so that he may compare the findings over a period—a delay that could be avoided if each candidate were offered radiographic examination on entry to the country and the film (with the candidate's permission) were placed at the disposal of any mission, whose doctor could then compare this first film with that taken when the candidate presented himself. Impartial medical advice at the outset, on the basis of the first radiograph, would spare some candidates months of wasted time and mounting anxiety.

The task of the mission doctors is to select the healthy, and naturally they tend to reject or defer any person with the slightest hint of tuberculosis. Last year the Australian mission in Austria examined 2045 persons and deferred or rejected 36 (about 2%) on account of the radiographic findings. The total examined by the Canadian mission was 2400, of whom 113 (about 5%) were rejected on this ground. Further investigation, if this were possible, might satisfy the mission doctors in at least some of these cases.

THE "HARD CORE"

In Austria, as in Italy, the emigration of the young and healthy has tended to raise the proportion of the elderly and less fit I C E M 's " caseload " in Austria of 26,000 includes about 6000 elderly or medically unfit and about 4000 socially unfit These are the " hard core "—some of whom are scarcely more likely to establish themselves in their first country of asylum than in another Their efforts are watched with frustration by those who want to help In the words of one experienced worker " *It takes as long to settle a single hard-core case as to organise the emigration of a thousand healthy people* ", while another declared that a social worker would be doing well if she organised the integration of two hard-core families in a month

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[7] The cost is shared by I.C.E.M., the Austrian Government, the Government of the recipient country, and in many cases U.S.E.P.

Elderly and Medically Unfit

Those rejected because they are over-age are especially difficult to settle Often they have a trade for which no local demand exists No longer resilient, they find it hard to adapt to a new language and new ways Thus a 57-year-old labourer refused the chance to emigrate under a special scheme to Norway, where materially his future would have been assured—probably because he could not bring himself to exchange the familiar *Gemütlichkeit* of Southern Europe for the more reserved mode of the North In this group are found both doctors and lawyers, who are the hardest of all to place no country wants them as such

The amount of medical unfitness is difficult to assess, but an I C E M survey of 12,000 in Austria two years ago revealed the following figures active or inactive tuberculosis, 500, mental disorder, 89, paralysis, 52, other chronic disorders, 72, partial blindness, 140, total blindness, 11, deaf and dumb, 48, amputees, 77, other physical infirmities, 386, vague and transitory disorders, 281, unclassified, 200

Socially Unfit

Austria has given a fine lead in establishing a home for unmarried mothers and their children, but otherwise only Sweden and the United Kingdom have accepted any of these The " unaccompanied " mother (whether her husband is dead, divorced from her, or still in the country of origin) is equally unlikely to be accepted, and yet, if only for the child's sake, this group should surely not be excluded

Likewise few countries have been willing to accept criminals Any person with a record of a crime, however small and however ancient, is generally debarred from emigrating A man who in a moment of heat struck an insulting relation of his former wife received a trifling sentence and thus disqualified himself from leaving Austria

Similar cases were recited in Germany Petty crimes, committed long ago and long ago deleted from the German register of crimes, prevent refugees from leaving the country Examples are blackmarketeering, collecting scrap metal without a permit, collecting cable in bombed houses, and insulting an official One worker in Germany suggested that a person with no crime recorded against him for three years should be regarded as having a clean sheet

ITALY

Italy has some 5000 refugees in seven official camps [8] and a further 15,000 who are more or less integrated in the community, though some 4500 are living at bare subsistence level and need continued help About 95% are Yugoslavs continue to cross the border into the country at the rate of 10–20 a day Their claim to refugee status is examined by a commission comprising 2 representatives of the Italian Government and 2 members of the U N H C R.'s office About 65–70% are accepted as refugees, some of the remainder are returned to Yugoslavia

Nearly all who remain seek to emigrate About 90% succeed (5000 left the country last year), the great majority going to Australia, the rejected 10% remain in the country

Some emigration schemes in Southern Europe are less attractive than others Under a scheme for selection of trainee gold miners for South Africa, the emigrant must undertake to stay at this work for at least four years, the penalty for breach of the undertaking being expulsion from the country

In Italy the refugee receives no money but is accommodated and fed by the Italian Government, at a cost of about 750 lire a day (there are about 1700 lire to the pound) According to some reports, the food in these camps is poor, but it appeared to be adequate Meat is served every day except Friday (when it is replaced by fish), and indeed there are authenticated reports of refugees in camps in the south selling their daily portion of meat to the less well-fed local people outside

Some of the camps are better than others, and that at Latina, in the Pontine Marshes, which is the " processing " centre for emigration, seems to be about as good and contented a place as any camp can be The attitude of the camp commandant largely determines the atmosphere, and in this camp the commandant is keenly interested and has done his utmost—for example, by pressing for amenities and by establishing a gaily coloured garden in the central compound—to diminish the bleakness associated with all such places

The refugee in Italy may with luck be given odd jobs in the camp, for which he is paid He is not supposed to work outside, but some in fact do find seasonal employment A refugee who has been in the country for three years may, if he finds permanent employment, secure a work permit, and he then gains all the social benefits of an Italian citizen Citizenship of the country can be secured only with difficulty and after a long time

U N H C R is running a camp-clearance scheme, for inclusion in which the main qualification is entry into the country before 1956 At the end of June, 1959, the 269 who qualified were of the following nationalities Yugoslavs (164), Russians who left their country before 1939 (25), Poles (21), Albanians (17), Bulgarians (12), Czechs (8), Hungarians (7), Russians who left their country after 1939 (5), Roumanians (4), Ukrainians (3), and Spaniard, Estonian, and Latvian (1 each)

At the end of this January 224 people qualified (two years ago the total was close on 600) Those who are not accepted by other countries U N H C R is trying to place in settlements—communities with care These settlements will never be entirely self-supporting, and will be a continuing charge on the Italian Government.

MEDICAL SURVEYS

Since September, 1959, I C E M has operated a continuous survey, including chest radiography on 100 mm film, of newly arrived refugees, all of whom go through the camp at Trieste (The Trieste camp, a converted warehouse, is far less satisfactory than that at Latina)

I C E M has also lately surveyed all in-camp refugees (For technical reasons children under the age of 12 were not examined radiographically) Analysis is not yet completed, but of 4467 examined radiographically, 64 single adults and 27 members of families were found to have active or presumably active tuberculosis Positive findings were reported to the camp doctors This survey should prove of great value, because, although the camp doctors make periodic physical checks, active tuberculosis has hitherto been brought to light in many cases only when the refugees have submitted themselves for emigration

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[8] These camps are at Trieste, Capua, Aversa, Farfa Sabina, Fraschette, St Antonio (nr Salerno), and Latina

GERMANY

If Germany has been left to the last in this report, it is certainly not because in that country refugees are fewer or their problems smaller than elsewhere According to U N H C.R., on July 1, 1959, non-German refugees under the High Commissioner's mandate numbered about 11,900 in 52 official camps Most had been there for ten years or longer

In 1957 a survey by the *Akademie für Staatsmedizin* in Hamburg showed that the official camps contained about 2200 "difficult" cases (i e., refugees who were old, sick, or handicapped, and in need of permanent care)

The estimated total outside official camps last July was 190,000, of whom 28,000 were unsettled They included about 11,000 "difficult" cases Many of those outside official camps live either in unofficial camps or in other grossly unsatisfactory places, such as cellars The vast majority in official camps and elsewhere are "old" refugees

HOUSING

Apart from the "difficult" cases, the great problem is housing except perhaps in Bavaria, which has a great concentration of refugees, no reasonably fit adult should find it hard to secure some sort of work.

In Munich alone, there are some 40,000 families on the "urgent" waiting-list for dwellings built by the local authority Of the 3068 dwellings completed last year, 1141 were reserved for German refugees

Between September, 1955, and the end of 1959, of a total of 1575 housing units planned under a special programme initiated by the United Nations Refugee Fund for refugees in official camps, 1154 had been completed Together with 1300 units planned under the camp-clearance scheme of U N.H.C R., the total is to be brought up to 2900 units U N H C R. is contributing an average of 25% of the cost, with a matching contribution of 75% from the Government.

Of the unofficial bodies, the Adoption Committee for Aid to Displaced Persons,[9] a non-denominational organisation, is doing outstanding work. Concentrating mainly on the "free-livers" in Bavaria, who are perhaps the worst-off of all, it is providing "key-money" to enable refugees to rent privately owned flats, with priority to those who have recovered from tuberculosis In addition it is largely financing the construction of a new home for the tuberculous who have been discharged from hospital but are not fit to take their chance in the community The Adoption Committee is the first organisation to have applied sizeable funds to the integration of those in unofficial camps, but now U N H.C R is surveying the numbers and needs of those in these camps—in preparation, it is to be hoped, for action.

SOCIAL BENEFITS AND MEDICAL CARE

In Germany the refugee who is unemployed or falls ill receives the same benefits as a German citizen. The great majority of refugees are employed, though the employment—especially of labourers—may be only seasonal. A labourer earns up to 400 D.M. a month (there are about 12 Deutschmarks to the pound), and if he is living in a privately owned flat, which will cost at least 150 D M a month, he will have difficulty in making ends meet.

After two or three years German nationality can be obtained Most, however, choose to remain Stateless—possibly because they hope eventually either to emigrate or to return to their homeland

In hospitals the refugee is treated on a par with a German citizen, and sometimes he is clearly better off in hospital than outside. For instance, at Gauting Sanatorium, near Munich, the tuberculous can serve a two-year apprenticeship as mechanics the workshops are beautifully equipped and well staffed, and failure to gain a diploma at the end of the two years is unknown. The refugee who gains such a diploma emerges as a skilled worker German sanatoria also house some middle-aged and elderly tuberculous refugees who have been there for up to ten years, the chronicity of their lesions perhaps being traceable to hardship in concentration camps or forced-labour camps, and to separation from friends and relatives and the conviction that no-one cares greatly how they fare

THE NEW REFUGEE

Those who come newly to the country as refugees are accommodated at Valka camp, near Nuremberg Originally built twenty-seven years ago for those attending Nazi Party rallies, it is in an appalling state The German authorities are alive to this, and by the end of the year it is to be closed and the remaining refugees transferred to the nearby Zirndorf camp, which is already partly built. Thus the worst and the best of the German official camps are cheek by jowl.

The decision as to refugee status rests with the courts, but where recognition is refused an appeal may be taken to first one higher court and then another—a process which may take up to three years It is unusual for an immigrant to be returned to his country after this time

Of the new refugees 90% are Yugoslavs Until their status is decided they are supposed not to take employment, but not uncommonly they engage in work without an official permit (so-called "black" work)

At Valka routine radiographic examination was instituted in 1950 but was later abandoned Last July it was resumed, and in order to gain full attendance the authorities have had to withhold meal tickets and pocket-money from those who fail to attend (This failure, it seems, is usually due, not to the refugee's fear of what may be found, but to his being absent and engaged on "black" work when the radiography unit visits the camp)

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[9] 227, Edgware Road, London, W 2

EMIGRATION

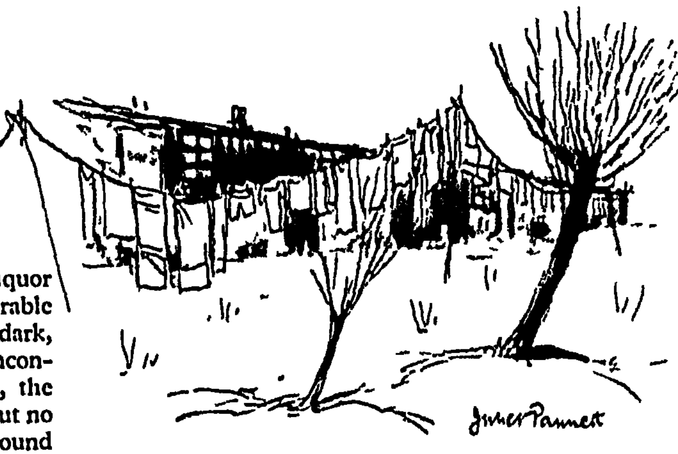
According to ICEM, UNHCR refugees who left Germany for resettlement elsewhere numbered 5243 in 1955, 8982 in 1956, 6967 in 1957, 1151 in 1958, and 2199 in 1959.

CAMPS IN GENERAL

"When you've seen one camp, you've seen the lot." The man who said this knew he was uttering a half-truth. Certainly the worst camps look and sound and smell depressingly alike: the bottle of liquor dropped by the alcoholic on the doorstep, the miserable dog which seems never to know where it belongs, the dark, dirty, creaking corridor, the mean rooms decorated incongruously with bright pictures from old magazines, the bunks strewn untidily with blankets, the old table (but no chairs), the acrid stench from the urinal, the sudden sound of a quarrel beyond the partition—these are the common denominators of camps at their worst. Camps also have basically the same atmosphere—an atmosphere of insecurity and isolation, as of a prison without bars. The visitor, wherever he turns, comes on little knots of two or three, standing or lounging on their bunks, exchanging gossip and rumours in subdued tones, and breaking off to regard the newcomer with uninquisitive wariness.

Those with knowledge say that in camps the attitude is basically paranoid.

This attitude does not necessarily derive wholly from the refugees' present situation. Strotzka,[10] in a close study of the Hungarian refugees, found two prevalent features. First, some had crossed the border with minds occupied by wishful thinking about what they would find beyond: miraculously this act was to end their difficulties. Secondly, some had a guilt-feeling about leaving home, akin to that of a deserter. Similar emotions may partly account for behavioural disorders in other "new" refugees.



The severity of the paranoia seems to vary from camp to camp: some camps have a much more oppressive atmosphere than others. (On the whole the farther south one goes in Europe the lighter is the atmosphere—perhaps because the southern peoples are more easy-going.) Obviously a main factor is the constitution of the group: one composed of people who have just arrived and are soon to emigrate will have a better atmosphere than one containing people who have lived long in the camp and have no hope of a solution. But other factors operate—for example, the attitude of the officials and the enthusiasm of the social and other workers.

Opinion is divided on the advisability of social workers being drawn from the ranks of former refugees. In some parts this is the practice, and the results seem satisfactory, the worker having insight into the refugee's attitude. On the other hand there is a risk of either over-identification with, or aggression towards, the refugees.

In a camp refugees have a corporate spirit, though not necessarily a healthy one, and this is reflected in toleration of behavioural disorders among their members. One cheering feature cannot fail to startle the visitor: the children mostly look healthy and happy, and talk readily enough to any who engage their attention. A possible reason is that, through propinquity, a closer mother-child relation is set up than is usual in more spacious surroundings. Children, it has been found, recover quickly from any ill effects of camp life, and through friendships at school they educate their parents in local ways; thus adults with children become fully integrated more quickly than the childless. For this reason it is especially regrettable that there are still some schools for the children of refugees only.

Protracted camp life can undoubtedly leave a mark, but Dr Hans Strotzka,[11] who has long experience, insists that behavioural disorders evaporate more completely and quickly when refugees move to reasonable surroundings than when an ordinary group of people are moved from slums to new estates. He finds refugees highly responsive to their environment.

SOME SPECIAL SCHEMES

Besides schemes for mass emigration of the healthy, special schemes for a limited number of the less fit have been applied from time to time.

Before the start of the World Refugee Year last summer, Sweden, Norway, and Denmark accepted groups in which individuals or members of families had active tuberculosis. Sweden also took some of the "post-tuberculous", and since 1954 it has taken more than 2300 "hard-core" cases. Belgium, Switzerland, and Luxembourg gave refuge to a few mentally disabled patients Refugees have been accepted also by France and the Netherlands

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[10] Strotzka, H. *in* Die psychohygienische Betreuung ungarischer Neuflüchtlinge in Österreich 1956–58 (edited by H. Hoff and H. Strotzka), p. 9. Vienna, 1958.

[11] Personal communication. *Dr Strotzka is surveying the mental state of refugees in Europe. The United Kingdom World Refugee Year Committee has guaranteed to meet the initial cost*

So far in the World Refugee Year, Canada has accepted 100 families with one tuberculous member, and Sweden 50 and Norway 15 families with handicapped members The United Kingdom has arranged to admit 200 handicapped, and it is sending a mission to select more—the total this time may be considerably greater than 200, and the conditions more liberal. Sweden is at present arranging to accept 50 families that include amputees or people crippled in other ways, and is provisionally arranging to accept a further 50 tuberculous families New Zealand has agreed to accept 70 handicapped families (including 20 from the European refugees in the Far East) Australia is undertaking a pilot scheme on the same lines

Some unofficial schemes, such as the Ockenden Venture, whereby children have been brought to this country, and a community plan in Sardinia, have proved highly successful.

In Sardinia a community, financed in the first place largely by Mr Don Murray, a film actor, was set up for the reablement of “ hard-core ” people, including alcoholics The aim is to make this community self-sufficient. Its members help to build their own houses, and otherwise engage in agriculture and chicken-farming Members of the Brethren Service Committee, a U S religious body, live in the community, which at present comprises 14 families the proposed total is 25 U.N H C.R. contributes 1 million lire for each family which establishes itself—and the great majority do, only a few failing and returning to the mainland. The scheme has the support of the Italian Government, which seeks to develop this formerly malarial island.

THE NEXT ROUND

This report is admittedly fragmentary the scattered facts it contains resemble a few tiny slices from a large apple—the slices, however closely scrutinised give little idea of the state of other parts of the apple. or of the size and condition of the apple as a whole. Nevertheless, from such facts as have been gathered and from instructive discussions with many people, a few conclusions can be reached.

MASS EMIGRATION

The mass-emigration schemes are applied mainly in the interest of the recipient country, which rejects families containing one or more disabled members

One family could not emigrate because the wife was myopic, another because one child had unilateral vision, a third because one of two children was deaf and dumb, and a fourth because the husband's mother was blind.

Such examples are readily multiplied. If each country relaxed its immigration laws to the extent of accepting families with handicapped members which could be expected to support themselves, that would be one step forward. The existing laws give rise to tension uncertainty, and distress in those who must decide whether part of their family shall emigrate and the rest remain. These laws are, moreover, out of date. The insistence on freedom from suspicion of pulmonary tuberculosis derives from a bygone age today tuberculosis can be regarded as a curable disease.

The U S.A., Australia, Canada, and the United Kingdom have partly relaxed their immigration laws in order to keep families together Other countries could do likewise with little risk of trouble or expense to themselves

In the U S.A. medical standards for refugees are the same as for others Exclusion of the tuberculous applies to aliens “ afflicted with tuberculosis in any form ” Under temporary legislation, adopted in 1957,[12] and extended in 1959,[13] this exclusion is waived for parents, spouses and children of U S citizens or of aliens who either have been admitted for permanent residence or have received an immigrant visa, provided satisfactory arrangements are made for medical care and supervision and for the support of the handicapped person. In 1961 Congress will review experience and consider further extension. At the end of last year, 2511 persons with tuberculosis had been admitted under this provision. Where the disease is shown to be inactive, history of tuberculosis is not a ground for exclusion. The only ground for exclusion on the basis of history alone is “ one or more attacks of insanity ” People in excludable medical categories may be admitted under discretionary provisions for medical treatment, or may be paroled under conditions prescribed by the Attorney General. The parole provision was applied to most of the Hungarian refugees who entered the U S.A. in 1956–57, later legislation changed the parole status to that of permanent resident for those qualifying after at least two years in the U S.A.

SPECIAL SCHEMES

In the planning and execution of special schemes for emigration the Scandinavian countries have played a leading part. If, as must be hoped, these schemes are to be multiplied, the criteria for inclusion might be made less rigid.

Under one scheme for the tuberculous, the conditions were that the affected person must be, not single, but a member of a family, that not more than one member of the family must be affected, and that the family must have *no* sponsor in the recipient country These three requirements excluded most applicants, the quota was not easily filled. and disappointment was caused to those who failed on one or another of the scores

The special schemes seldom cater for that promising group—the “ post-tuberculous ” (Sweden and the United Kingdom have accepted a few) It must seem a mad world to those—and they are many—who are rejected for mass-emigration schemes because they have a fibrosed lung lesion and for special emigration schemes because they do not have active tuberculosis

THE HARD CORE

Of those who have not hitherto been included in any emigration schemes the ageing and aged, the “ unaccompanied ” mothers, and some of the so-called criminals are in special need of help and acceptance

In one or two of the first countries of asylum only manual work is to be had, and the over-40s who are unfit for this can look forward only to eking out the years until they qualify for an old people's home. In at least one country such homes are wretched places, without privacy, comfort, or sympathy

The unaccompanied mothers (of whom a few have been accepted by Sweden and the United Kingdom) need help, first on the humanitarian ground that without a husband they are at a disadvantage in rearing their children, and secondly for the social reason that a new generation of Stateless people in Europe should be avoided. If they became pregnant while they were unmarried refugees, that is no token of promiscuity “ Having babies,” said one worker, “ is a camp disease.”

Some “ criminals ” must be convinced that all hands are turned against them. Who shall say that a man whose only penal record is a short sentence in 1946 for insulting a German official is necessarily unworthy of citizenship? Yet no country has wanted him.

The United Kingdom, it seems, now denies entry only to habitual criminals In the U S A. an alien “ who is excludable because of the conviction of a misdemeanour classifiable as a petty offense by reason of the punishment actually imposed ” may now be admitted[14]

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[12] Public Law 85-316, 85th Congress, S 2792, Sept 11, 1957

[13] Public Law 86-253, 86th Congress, H.R 6118, Sept 9, 1959

[14] Immigration and Nationality Act, p 25 Washington Government Printing Office, 1958

The "hard core" are not necessarily a burden on the country where they settle in Norway 95% of this group are self-supporting

ORGANISATION

In the exodus from Hungary no fewer than 85 organisations contributed to the care and movement of the refugees In Europe today the number is smaller, but it is still great enough to cause confusion and delay In Germany, particularly, the need for a central organisation was repeatedly emphasised Yet this unity is unlikely to be easily achieved because some agencies, though staffed by dedicated workers, are jealous of their independence and of the numbers in their care (the sums payable from official funds are related to these numbers) As it is, registration with two or even three different agencies is not uncommon

The unhealthy and unfruitful competition in refugee work, though possibly inevitable, might be abated by bringing together at one place and at one time all concerned with the well-being of the refugee—the representatives of international, national, and voluntary organisations

Each new refugee might be directed to a central depot, where he would be examined by an independent doctor and have his chest X-rayed If the refugee wanted to emigrate under a mass scheme but the X-ray showed evidence of changes likely to preclude this, he could be told, and, if he disbelieved what he was told, he could go to the mission doctor, in the same building, with the radiograph If he failed here and with other missions, he might be advised to seek entry into, say, Sweden, under a special scheme Deciding, instead, to stay in the first country of asylum, he would go to the representative of the labour office, in the same or a nearby building, who could tell him at once the prospects of employment in his trade The doctors, working close to the voluntary agencies, could inform the relevant agency without delay of what was needed medically to fit a refugee for work in the same country or for acceptance abroad—perhaps a pair of spectacles a prosthesis, or a fairly small operation

Such a scheme would involve no added expense beyond the cost of the refugee travelling to and from the centre By bringing together all resources at the same time, it would enable the refugee to decide in one or two days (instead of, as in some instances at present, one or two years) where he should go and what he was to do, and it would help to bring to light the "best" solution and not just "a" solution

The liaison between the medical side and the voluntary agencies seems to be particularly defective A sturdy man who was fit but had years ago had an amputation at the wrist was lately accepted under a special emigration scheme after having done not a day's work in his fifteen years as a refugee A prosthesis would almost certainly have made this long period less barren of work and hope

"Emigration processing centres" have already been established at Latina in Italy and at Salzburg in Austria Central "processing" might also usefully be applied to those who have been in the first country of asylum for some time without being integrated But any such scheme can be instituted only with the support—and perhaps at the behest—of the national Government

THE UNITED KINGDOM'S PART

The greatest immediate needs in Europe are, first, for more money and, secondly, for further skilled social workers and integration counsellors to ensure that the money is well spent

Not many declare that they wish to settle in this country The quota for 2000 fit immigrants to the United Kingdom, under a scheme started in 1953, was filled only last year Of 1467 "new" Hungarian refugees in Austria who were asked to name their country of first choice, only 17 named Britain (The favourites were the U S A, Australia, Canada, Germany, Sweden, and South Africa, in that order) But any such list, as has been said, is misleading If the same 1467 had been told "You may go to settle in the United Kingdom on Tuesday week", many more than 17 would have eagerly accepted To the refugee abstractions mean little only specific offers bring to light what he is willing to do

As has already been mentioned, the number of handicapped admitted to this country is likely soon to be increased substantially [15] Two groups who deserve special attention are the tuberculous, and the post-tuberculous who are at present mostly barred from emigrating to Australia or Canada under mass schemes (Some, in whom the disease had been quiescent for at least two years, were admitted to the United Kingdom under the "2000" scheme, and under the "200" scheme a few patients with active tuberculosis have been selected)

The United Kingdom might offer to accept the "post-tuberculosis", and their families, on the understanding, reached with the two Commonwealth Governments, that if further investigation should confirm that the chest condition was satisfactory, or if the condition was made satisfactory by treatment, they would be accepted by one or other of these countries A few would, despite treatment, fail in the end to satisfy the requirements of these countries—a risk which would have to be made clear to the families concerned This country should surely be willing to give asylum to these few Many more would be enabled to settle in the country of their choice

Such an effort by the United Kingdom would be a small practical step towards relieving the overburdened first countries of asylum Other possible measures are discussed in a leading article on p 475 of this issue

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Many have cheerfully set aside their own work for minutes, hours, or even days to supply information for this review We are especially indebted to the following

In London Monsieur René Dutilleul-Francœur, representative in the United Kingdom of U N H C R, Dr C A Boucher, senior medical officer, Ministry of Health, Dame May Curwen, chairman, and Miss M Holmes à Court, general secretary, British Council for Aid to Refugees, Mrs F C Rigby, chairman, and Mrs Erica Linton, secretary, Adoption Committee for Aid to Displaced Persons

In Geneva Dr Hans Strotzka, mental health adviser to U N H C R, Dr K G Watson, chief medical officer, I C E M

In Rome Dr E Schlatter, representative in Italy of U N H C R, Dr G B Watkins, of I C E M

In Vienna Dr Gertraud Voekel, of the Ministry of the Interior, Mr K C Elliott and Mr W K McCoy, of U N H C R

At Linz Mr Arne Torgersen, of U N H C R

In Salzburg Mr J L Carlin, Dr Cleve Schou, and Monsieur Roger Walon, of I C E M

In Munich Mr M E Ettmuller, of U N H C R, Mr Ronald Watson, of the Adoption Committee for Aid to Displaced Persons, Miss Shelagh Armitage, of the Women s Voluntary Services

At Gauting, Bavaria Dr Hubert Tuczek, medical director of the sanatorium, Frau Irmgard Neumann, chief social worker at the sanatorium

At Nuremberg the Commandant of Valka Camp, Fraulein I Semerssner, of the U N H C R office at the camp

In Bonn Mrs S Lennox, of U N H C R

None of the errors in this account, and none of the opinions (except where these are specifically ascribed), should be associated with those named here

The illustrations are by Juliet Pannett, S G A

Copies of this article (1s each) may be obtained from The Lancet, 7, Adam Street, London, W C 2 All monies received in this way will be sent to the United Kingdom World Refugee Year Committee

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[15] See *Lancet*, Feb 13, 1960, p 393

In England Now

A Running Commentary by Peripatetic Correspondents

AFTER addressing envelopes for several hundred reprints I have been impressed by the length of the American addresses This is the kind of thing I have been writing most of the day

Waldo P Whattamouthful, Junior, M.D ,
(Director of Polysyllabics) #4231,
The Medico-Psycho-Idiopathic Centre,
Bureau of University Medical Services,
The Croesus L Goldendough Memorial Foundation,
The University of North Jabberwocky,
1234, East 49th Parallel Street,
Jabberwocky City, 23,
State of Louis Carrolina, U S A

But every now and then my cramped writing hand gets a chance to recover when I write an English address

B Brief, Esq , M D ,
Barts Hospital

* * *

Here I and sorrows sit Here is my throne, bid kings come bow to it. That was the gist of Connie's reply to our public-convenience cleaner He is a mild inoffensive little man, with a half apologetic air, as indeed befits the duty of his calling upon both sides of the island refuge in our market square Constance is made of sterner stuff and knows her rights down to the last pennyworth she behaves like the dowager queen of a far-flung realm. But she will insist on spending her nights in our public convenience We would not mind if she just curled up quietly to roost in the end cubicle we would leave the door ajar and lay at her disposal the full range of our social service Constance has her own ideas about community care, she has money of her own in the purse beneath her skirt, she has travelled the world and still likes England best· She must be nearly seventy and she is fond of fish and chips The trouble is that fish and chips are wrapped in newspaper, and newspaper is as tough as Connie If we have had to rod that drain once we must have done it twenty times

When she came into winter quarters with us last year she was willing to live and let live, but, like the permanent residents in a guest-house, she has become over-possessive and almost proprietorial. The electric light bothers her eyes in the evening, so she climbs up and removes the bulb Our other guests have to fumble their urgent way with matches or a torch, and then Connie puts on a deep gruff voice and startles them out of their wits with a torrent of words that are usually only written in such places We get indignant demands for money back next day, and wild accusations about the morals of our town. Once tucked in for the night Connie will not come out. We called the police. One of our new policewomen tried chirping through the door for ten minutes, and then went back for the sergeant. He brought a scaling ladder and had the advantage of a face-to-face discussion across the cistern Constance rested her case upon the common law of England As one of the public, she found it a great personal convenience to enjoy in the fullest sense the unlimited value of what she had paid the proper price for The police retired defeated and said it was our pigeon. The cleaner suggested squirting his hosepipe underneath the door, but luckily I phoned the Town Clerk first. He mumbled something about assaulting an invitee and advised against it So Constance, flushed with success, remains our paying guest She says she is thinking of moving at Whitsuntide to one of the seaside towns The cost of living remains the same wherever she goes no bother about hotel bookings England is her realm, and she seems enthroned for life

* * *

Down the corridor I have a neighbour who, I suspect, has lost half his colon, like me, and is enduring the rigours of cloacal rehabilitation. We share the services of a one-nurse-power 1959 model tubular-framed wheeled bedpan carrier whose reassuring presence in the room is replaced by a sense of grievous need when he wins it from me I suppose he feels the same The red banner permanently placed over the bedpan seems to be of historic significance, I suppose the vehicle was not covered by the Act of Parliament which replaced the famous "Red Flag Act" Incidentally no bell, siren, or hooter is fitted, all warning noises being provided by the driver This feature is not even to be found in the annual veterans' trip from London to Brighton.

* * *

Veterinary surgeons attempting to medicate rhinoceroses meet high consumer-resistance, because their patients, though well down the list of potential passengers in lunar probes and similar rocket-propelled television sets, have lamentably little confidence in the progress of science This unhealthy attitude of mind has been countered at the San Diego Zoo by a vet who uses a rifle and plugs the intransigent reactionaries with medicated bullets

The reluctance of rhinoceroses to swallow strange chemicals is in awesome contrast with the habits of that Lord of Creation and Nature's Noblest Work, *Homo sapiens*, who pours such substances down his gullet like coal down a chute If threatened with medicinal bullets, he would probably charge the guns in the manner of an ecstatic Fuzzy-wuzzy storming a British square

Nevertheless, for the G P , though his visiting-list makes him feel more like shooting himself than his patients, but only just, missile therapy could hold certain attractions Sitting happily at the butts in his consulting-room, the patients would be propelled from a trap across the room and out through the front door The really pukka practitioner would of course not fire until he could see the whites of their gluteus maximus, and unsporting habits like potting the sitting clients would be anatomically impossible

Invitations to colleagues to come over and shoot—"Make it a Monday, easily the best day I've 1500 brace on my list"—would be eagerly sought after Going on safari after patients, and "sitting up" for the craftier varieties in trees under which has been tethered a 16-oz bottle of tonic, offer interesting possibilities, and how expeditiously one could empty a crowded waiting-room by loading with every pill in the sample-drawer, hurling open the door, and administering what in Nelson's day was known as "a whiff of grape"

* * *

We were prepared to think that our children believed that all human activity centred around hospitals, just as Daddy's did, but we did not realise that the belief extended to the animal world We were on our first holiday in Australia and walking along a red dirt road listening to the new bird songs Suddenly we came across a large lizard lying inert in the sand with its head obviously crushed by a passing tyre Jan, aged three, said accusingly, "That poor lizard is dead, Daddy You must have run over him with the car" We denied this, but the inquisition continued. "Was it a Mummy lizard or a Daddy lizard?" Empirically we declare it male "Why did he get run over, Daddy?" Here we offer some propaganda for road drill "He could not have looked both ways before he crossed the road" "Why did he not look both ways before he crossed the road?" Desperate now—we groan, "Perhaps he was hurrying home from work." "What hospital did that lizard work at, Daddy?"

* * *

Civil Service Glossary for newcomers to the National Health Service

"The position is fluid"—Everything is in a dreadful mess

"The position is being carefully watched"—Nothing whatever is being done

"The matter is not yet finalised"—Nothing has even been started, although there's a lot down on paper

"A small committee is being appointed to look into the matter"—We're hoping this will keep everyone quiet for a year or two

"Please clarify your remarks"—You are expected to use plain English, even if we don't have to

"Constructive criticism is welcomed"—*We're not interested in* any of your silly ideas

* * *

REQUIEM

Alas! Poor Spens beyond our range
To Limbo has been sent
We swore that we would take no change
But now our Spens is Spent

Letters to the Editor

PRIVATE PATIENTS IN THE NATIONAL SCHEME

SIR,—Your views on the subject of drugs for private patients seem strangely confused Having stated that "within the National Health Service, medical privileges cannot be bought" you add "The apparent exception—the private bed in a hospital—is not really an exception at all the patient in a pay-bed is paying at least the full cost of his treatment" Perhaps one may ask why you have omitted that other exception, the amenity bed, in which privileges are "bought" at considerably less than cost price

You aver that the doctor's time and convenience of access to him are an important part of good personal care and that *the commonest criticism of N H S general practice is that it fails to provide these things* (my italics) You then go on to state that such medical care should be "provided not sold" But surely all medical care, whether secured privately or by compulsory insurance and taxation, is "bought" and, by the same token, "sold" Following these confused imputations about buying and selling you go on to suggest that the private doctor is "selling care of a higher standard" If this be so (and if *The Lancet* is really interested in high medical standards as opposed to budgetary semantics) then surely it is to be encouraged

A lot of rubbish has been talked about *two* standards of medical care (chiefly emanating from the Socialists and echoed by the Cohen Committee) when there are manifestly many different standards both in State and private practice Good State Medicine may be better than bad private practice, but good private doctoring tends to be better than most State doctoring for good Medicine takes time and time costs money If the State is unwilling or unable to provide the G P with more money and proper incentives then any sane Government should be grateful that some patients are keen and willing to do this themselves Despite all the impediments placed in their way many patients do, to their credit, prefer to exercise some measure of personal responsibility for their medical care To help those who are thus prepared to help themselves seems both sound finance and sound philosophy

You, Sir, seem concerned that higher standards in private practice will show up some of the defects of N H S doctoring Far from this giving anyone, as you suggest, a vested interest in preserving the defects of the N H S (and defects exist in private practice too) it must surely encourage higher standards all round Certain it is that improvements in the conditions of N H S practice are more likely to come about if capitation-fee Medicine has to stand up to lively competition from private practice The present near-monopoly by the State is surely contrary to the best interests of British Medicine

London, W 1 REGINALD S MURLEY

SIR,—The argument that a fee-for-service system of payment is anathema to the N H S seems unreasonable It already exists for obstetrical work, domiciliary consultations, and the use of an electrocardiograph It seems a pity to reason the case from false premises

I fear "two standards of care" are already firmly built into the N H S, so long as the conscientious doctor is financially poorer by the more care and attention he gives his patients

He has the choice of being financially solvent with an uneasy medical conscience, or financially straitened with a clear medical conscience I think most doctors actually working a practice will agree with this unpalatable fact, ignored by administrators and politicians

Hurley, near Ringwood
Hampshire
R HOWARD

SIR,—You rightly stress in your editorial note on last week's letters that the amenities of the ordinary list should be improved But would you not agree that it would be reasonable for the occasional patient to pay a fee for the privilege of being seen in his own home, or under conditions of greater comfort and privacy, for any minor disorder for which he might otherwise be expected to attend the surgery?

Workington R N R GRANT

SIR,—As a private practitioner I already make use on behalf of my patients of the consultant, radiological, pathological, and other specialist services provided by the State at their expense, and my signature suffices to secure them the sick benefit, maternity grants, and so on to which they may be entitled, I cannot, therefore, follow the reasoning in your annotation of Feb 13, that to obtain their medicaments for them from the same source, and to undertake to conform with the modest standards of economy and propriety in prescribing expected of doctors in the N H S, would introduce an entirely new relationship with the latter, and involve, as you put it, entering the Health Scheme

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It is because autotransfusion is, curiously, so often regarded with incredulity that I feel it a duty to demonstrate the method to my students who may, in time to come, practise in regions where blood-banks are unknown I bear with fortitude their remark that, being a Scotsman, I cannot endure seeing blood wasted

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The rapidly rising standard of pharmaceutical education today, with its emphasis on pharmaceutical chemistry, pharmacology, and therapeutics, is equipping the pharmacist for his true professional role—that of a recognised authority on the chemistry, actions, and uses of new drugs New medical products are becoming increasingly complex both in their chemistry and usage. There will, therefore, be greater need than ever, in the years ahead, for knowledgable pharmacists in retail practice and in hospitals to make a detailed study of new drugs and to make this knowledge available to the medical profession, to help them choose the best therapeutic agent once a diagnosis has been made I am certain that there are, even today, many retail and hospital pharmacists who are living up to the highest professional standards in providing just such a service

The pharmacist of tomorrow will be even better equipped to render this service, and I feel that Dr Miller and Dr Smith are doing a great disservice to their own profession as well as to pharmacists in general by giving the impression that there is no more to pharmacy than the counting of N H.S tablets Even in the dispensing of tablets the vigilant pharmacist uses a great deal of professional knowledge, for he is the last line of defence between the patient and the wrongly written prescription, of which there are perhaps more than the medical profession are prepared to admit Unfortunately one seldom hears of this important aspect of the pharmacist's work, but it is one which will undoubtedly become even more important and necessary as drugs become more and more potent and specific in their actions and hence more dangerous if prescribed or dispensed wrongly

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SIR,—The appeal for volunteers for a trial of oral contraceptives (the Pincus pill) in Birmingham recently has resulted in a spate of letters from doctors all over the country asking for further particulars about the pill and its use May I through your columns give an outline of the pill, the present position, and the future possibilities?

There are a number of orally active progestational steroids now available. In addition to their uses in endometriosis, menorrhagia, subfertility, &c., they can be administered in such a way as to inhibit ovulation. One of them, norethynodrel, has been used extensively first by Pincus and his colleagues in Puerto Rico and since then by Tyler and others

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Further studies are essential to find out the long-term effects and the effects on the menopausal woman (as withdrawal bleeding takes place each treatment month, the normal amenorrhœa of the menopause is masked it is believed, however, that the menopause is not postponed and that the decrease in primordial follicles with age is not affected by administration of these steroids)

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The pills are administered in the doses given above (though smaller doses are now being tried) daily from the 5th day of the menstrual cycle for 20 days This will normally be followed by a withdrawal bleeding If breakthrough bleeding occurs (that is, during administration) it seems best to stop and allow a withdrawal bleeding, regard it as an early menstrual period, and commence administration again on the 5th day for 20 days If menstruation is delayed beyond 8 days after the drug is finished, it must be given again as if menstrual bleeding has occurred. Very often, though there are irregularities in

Letters to the Editor

PRIVATE PATIENTS IN THE NATIONAL SCHEME

SIR,—Your views on the subject of drugs for private patients seem strangely confused Having stated that "within the National Health Service, medical privileges cannot be bought" you add "The apparent exception—the private bed in a hospital—is not really an exception at all the patient in a pay-bed is paying at least the full cost of his treatment" Perhaps one may ask why you have omitted that other exception, the amenity bed, in which privileges are "bought" at considerably less than cost price

You aver that the doctor's time and convenience of access to him are an important part of good personal care and that *the commonest criticism of N H S general practice is that it fails to provide these things* (my italics) You then go on to state that such medical care should be "provided not sold" But surely all medical care, whether secured privately or by compulsory insurance and taxation, is "bought" and, by the same token, "sold" Following these confused imputations about buying and selling you go on to suggest that the private doctor is "selling care of a higher standard" If this be so (and if *The Lancet* is really interested in high medical standards as opposed to budgetary semantics) then surely it is to be encouraged

A lot of rubbish has been talked about *two* standards of medical care (chiefly emanating from the Socialists and echoed by the Cohen Committee) when there are manifestly many different standards both in State and private practice Good State Medicine may be better than bad private practice, but good private doctoring tends to be better than most State doctoring for good Medicine takes time and time costs money If the State is unwilling or unable to provide the G P with more money and proper incentives then any sane Government should be grateful that some patients are keen and willing to do this themselves Despite all the impediments placed in their way many patients do, to their credit, prefer to exercise some measure of personal responsibility for their medical care To help those who are thus prepared to help themselves seems both sound finance and sound philosophy

You, Sir, seem concerned that higher standards in private practice will show up some of the defects of N H S doctoring Far from this giving anyone, as you suggest, a vested interest in preserving the defects of the N H S (and defects exist in private practice too) it must surely encourage higher standards all round Certain it is that improvements in the conditions of N H S practice are more likely to come about if capitation-fee Medicine has to stand up to lively competition from private practice The present near-monopoly by the State is surely contrary to the best interests of British Medicine

London, W 1 *REGINALD S MURLEY*

SIR,—The argument that a fee-for-service system of payment is anathema to the N H S seems unreasonable It already exists for obstetrical work, domiciliary consultations, and the use of an electrocardiograph It seems a pity to reason the case from false premises

I fear "two standards of care" are already firmly built into the N H S, so long as the conscientious doctor is financially poorer by the more care and attention he gives his patients

He has the choice of being financially solvent with an uneasy medical conscience, or financially straitened with a clear medical conscience I think most doctors actually working a practice will agree with this unpalatable fact, ignored by administrators and politicians

Burley, near Ringwood
Hampshire R HOWARD

SIR,—You rightly stress in your editorial note on last week's letters that the amenities of the ordinary list should be improved But would you not agree that it would be reasonable for the occasional patient to pay a fee for the privilege of being seen in his own home, or under conditions of greater comfort and privacy, for any minor disorder for which he might otherwise be expected to attend the surgery?

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These difficulties, plus the present expense and the fact that the tablets must be taken regularly or bleeding occurs, or fertility may increase, mean that they are not really suitable for prescribing at present They seem to be reasonably efficient if taken faithfully Pincus' investigations gave an all-over efficiency of 70%, but he claims that only one pregnancy occurred among those women who had taken the pills exactly as directed

While the development of these steroids as oral contraceptives is a most interesting step forward in the search for simpler contraceptives, it seems at present that they are not what we are all looking for something much simpler, much less expensive, and preferably with a chemical and not a hormonal action, would be preferable if it is to be used on a large scale to deal with the enormous problem of rapidly expanding population in underdeveloped countries

May I make it clear that these trials are quite separate from the normal working of the Family Planning Association clinics Patients who attend F P A clinics will continue to receive advice on maximum safety methods of contraception

London, S W 1

ELEANOR MEARS
Medical Secretary, Family Planning Association,
Medical Secretary, Council for the Investigation of Fertility Control

WHAT IS A TRANQUILLISER?

SIR,—May I propose that we adopt the following definition of the word "tranquilliser"?

"A tranquilliser is a drug produced to compete commercially with chlorpromazine, which has no unequivocal therapeutic efficacy, which aggravates the risk of suicide by its depressant action or creates the risk of addiction by its euphoriant effect, and which, by masking the signs, tends to interfere with the recognition of early psychotic states"

Hartwood Mental Hospital,
Shotts, Lanarkshire

L N COOK

FATALITIES AND SPORT

SIR,—Dr Taylor (Feb 20) is teasing you This would doubtless be amusing were it not for the possibility that some of your readers, who perhaps have not been following the argument, might be deceived into thinking that he really means what he says

From ancient days it has been accepted by the common law of England that it is not the act itself, but the wrongful intention that prompts it, which determines whether or not blame may be laid upon the doer The law also presumes that a reasonable man must be taken to intend the natural and probable results of his actions Both these are in accordance with common sense and the usages of civilised communities

In every sport except boxing injury is accidental in the sense that it is sustained against the rules or in spite of them In boxing the avowed intention is to produce injury, and having done so, to exploit it until the injured man is effectively defeated, The London Amateur Boxing Association's recent handbook, *Medical Aspects of Amateur Boxing*, is commendably frank in this regard On p 12 it is stated without equivocation that "Injury to the cranium and its contents is a direct product of boxing and *not an accident as in all other sports*" (Italics not original) An act does not have to be unlawful before it can be recognised as totally unjustifiable

Of course a death in any sport is to be deplored. But an accidental death in the course of a game of rugby football is rather a different matter from a death in the boxing ring The rules of rugby do not condone deliberate injury, the rules of boxing facilitate, and are designed to produce, deliberate injury That is why many of us think that boxing should be prohibited whilst not in any way wishing to interfere with other sports There is no inconsistency here

It is true that some people evidently find it difficult to grasp the underlying principle This places a special responsibility on us all not to create confusion in their minds on purpose

Godalming

J A WALCOTT

SIR,—In rugby football injury is accidental In boxing it is deliberate

London, S E 5

F B BYROM

CASUALTIES AND CASUALS

SIR,—I am in complete agreement with Dr Doyne Bell (Jan 30) that casualty departments should be renamed "accident and emergency departments"

At the North Lonsdale Hospital, Barrow-in-Furness, and at Preston Royal Infirmary, the cases dealt with in the casualty departments are restricted Both hospitals contend that "consultation and treatment in this department are intended for (1) recent accidents, (2) urgent cases of collapse, &c., and patients referred from their own doctor by letter" (There are notices to this effect outside each department)

In Barrow we include under recent accidents those which occur after the general practitioners' evening surgery and who attend hospital up to 10 A M the following day If the patient has been sent by his own doctor with a condition that is not urgent, he is referred to the next appropriate outpatient clinic.

Patients who do not come into the above categories are referred to their own doctor with a printed letter stating that the case is not considered an emergency Exceptions are made for patients who would suffer hardship by doing so, and for all eye cases During the day the "sorting" is carried out by the clerk in charge of the casualty records with advice from the casualty officer

The age-distribution and sources of new patients are similar to Dr Fry's series but a comparison of diagnostic classification cannot be made without breaking down his figures still further The only type of medical or surgical patients seen in the department are those who have collapsed at work or in the street, &c, because patients sent by a local practitioner are admitted directly to the wards concerned and *not* through casualty

Analysing our figures we find that 30% of casualties have wounds which require two or more sutures, 14% are limb fractures, of which half involve wrist and hand, 13% are foreign bodies in eyes, and 10% are contusions and 4% sprains 57% of new attenders arrive within 2 hours of the accident and another 14% within 24 hours

As a result of their first attendance 60% of patients were discharged, all of whom had been given a letter for their own doctor 3% did not reattend when asked to do so 7% were admitted, and the remaining 30% reattended (two-thirds of these once only) This last figure would be smaller, but a "standing order" in this hospital is that those cases not seen by the casualty officer himself must reattend to see him or the consultant in charge of the department Half the reattenders were referred to other outpatient departments

In support of Dr Fry our figures show that 33% of cases seen in casualty could only have been dealt with there, but 40% could have been treated by the G P and 5% by a nurse only

To save the more "regular clients" many injections of A T.S and the wait thereafter, all those given A T.S are recalled 6 weeks later for tetanus-toxoid immunisation The aim is to immunise the local working community and children 80% of these patients do attend for the course and since the scheme started two years ago[1] over 2000 have been immunised (more detailed figures will be published soon)

This casualty department is staffed by a casualty officer, who is also the orthopædic registrar, and in his absence, by the house staff, though he is available if required There is a consultant orthopædic surgeon in charge, who does four 1-hour sessions a week in the department reviewing certain cases, including some of the fractures

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[1] See *Lancet* 195[illegible] i, 1176

General practitioners have direct access to the X-ray department, but perhaps do not use this facility to the fullest advantage Those of their patients who have fractures are automatically referred to casualty by the radiologists after they have seen the wet films As the waiting lists for outpatient appointments are not large, except in the ophthalmic department, casualty is not often used by the local doctors as a short cut to outpatient clinics

I agree entirely with Dr Fry on his views as to the future of the casualty department. The number seen has increased and the main reasons are probably (*a*) there is a 24-hour service, (*b*) there seems to be a general belief amongst the public that even the most trivial injury should receive hospital attention, (*c*) the attitude "we pay for it so let us have our money's worth" Most of us who were children before the war would never have been sent to the hospital or even to our doctor with the minor trauma which today is often seen in casualty departments

North Lonsdale Hospital,
Barrow-in-Furness

P A. GARDNER.

INFANTILE STRUCTURAL SCOLIOSIS

SIR,—Mr Denis Browne (Feb 13) criticised the incompleteness of your annotation of Jan. 30 I should like to support your main point—that further knowledge of the ætiology of this condition is the most essential requirement for improvement in methods of treatment.

It might perhaps have been worth mentioning that 80% of infants have a lateral curve of 10° or more at 6 months, 46% at 12 months, and 7% at 18 months, the normal stimulus of assuming the erect posture apparently being the factor leading to correction of this type of curve [1] The existence of a resolving type of structural infantile idiopathic scoliosis, as distinct from the progressive variety, was first described in a paper published in 1955 [2] Further evidence has more recently been published of resolution in older children,[3] and discovery of the cause of resolution would certainly be an important advance in our knowledge of the ætiology and treatment of idiopathic scoliosis Although Harrenstein[4] described the recovery of a limited number of very young patients with lateral curvature of the spine he, as others have done, attributed it to a form of treatment.

Those interested in the subject would be grateful to Mr Denis Browne for producing any evidence that progressive infantile scoliosis can be cured in early infancy by "splinting and physiotherapy"

Nuffield Orthopædic Centre,
Headington, Oxford

J C SCOTT

CATHETER DRAINAGE AND INFECTION IN ACUTE RETENTION OF URINE

SIR,—We entirely agree with Mr Harrison (Feb 20) in preferring the Gibbon catheter to the ordinary rubber and plastic catheters for bladder drainage.

However, the work which we reported on Feb 6 was started before the Gibbon catheter became available, and finished more than a year ago It had as its principal object the evaluation of closed drainage in the treatment of acute retention of urine We wished to test the effect of preventing the ascent of contaminated air-bubbles in the drainage tube, uncomplicated by a change in the type of catheter used For this reason, we continued to employ the latex and plastic catheters (size 18 and 20 F) which were in routine use when we began our investigation.

In the periods of up to a week or so for which our patients were drained, urethritis was not severe enough to necessitate changing the catheters and closed drainage gave excellent results, as we have shown. However, the Gibbon catheter is preferable even for short periods of drainage, and is especially preferable for longer periods We now use it routinely, but should perhaps say that the Gibbon catheter is not suitable for draining the bladder immediately after prostatectomy The narrow lumen is readily blocked by clot. For postoperative drainage we now employ a boilable 'Neoplex' catheter (size 22 F) in conjunction with the apparatus for closed drainage and irrigation which we described in 1958 [1]

Department of Pathology,
Bristol Royal Hospital,
Royal Infirmary Branch,
Bristol

ASHTON MILLER
W A GILLESPIE

ANTI-SMOKING CAMPAIGN

SIR,—Thank you for the space you gave to the interesting account (Feb 6) of the commendable anti-smoking campaign by the Edinburgh Public Health Department Such a campaign is bound to make an impact whose value cannot be immediately assessed But there are, I suggest, two lessons to be noted.

First, a national habit can be adequately faced only on a national scale. Edinburgh has given a noble lead But its example has been largely offset in the minds of smokers (who are, of course, on the lookout for an excuse to continue their habit!) by the lack of such a lead elsewhere As doctor after doctor has written to our Society to say, this thing demands a central lead and a national campaign. All honour to Edinburgh Public Health Department for their splendid local lead! But none to the Ministry of Health for the national lead they have not given!

Secondly, we are confronted with a vicious circle—or more than one Warning boys and girls against smoking must be reinforced by parental example. But adults who are enslaved by the habit cannot give such an example. Over 4000 such adults have written to our Society pleading for help to free themselves from this slavery But when they *have* managed to succeed, they are confronted with an environment in which smoking is still allowed in almost every public place, so that they find themselves almost forced to resume smoking in self-defence. On top of this, of course, there are the massive advertisements and vested interests ranged against us, while the anti-smoking forces are weak and impoverished.

The National Society of Non-smokers is trying to curb cancer by curbing (at every turn) what has been identified as a main factor in the increased lung-cancer mortality We are seeking to warn society, curb smoking, deter youth, protect non-smokers, free "smoke-slaves" We shall gratefully welcome the moral and financial support of new members

138, East Dulwich Grove,
London, S E 22

HUBERT V LITTLE
Secretary,
National Society of Non-smokers

SIR,—The conclusions of the Edinburgh investigation (Feb 6) are what might have been expected The position would be much the same with other drug addictions if dealt with as timidly and respectfully Would exhortations, lectures, &c, have much effect on the use of heroin, cocaine, and opium if their manufacture, advertising, and purchase were free and uncontrolled ?

It would be refreshing to see the Ministry of Health return to earlier public health traditions, when abuses were boldly dealt with. Nowadays the Ministry seems to hang back if there is any question of antagonising public ignorance and apathy, or offending powerful advertising, industrial, or other vested interests

London, W 8

G G SHERRIFF

SIR,—All such campaigns go about it the wrong way The expected response of most people, especially the young, to statistics about the ill effects of smoking on health in middle life and old age will be "We, as a nation,

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1 Scott, J C *Proc R Soc Med* 1956 49 398
2 Scott J C, Morgan T H *J Bone Jt Surg* 1955, 37B, 400
3 Scott J C *ibid* 1959, 41B 105
4 Harrenstein, R J *Rev Orthop* 1936, 23, 289

1 *Lancet* 1958, ii, 608

prefer to die on our feet rather than live on our knees " What is needed is subtle build-up of the non-smoker and smirching of the smoker statements or proof that the cigarette is a substitute for a dummy or a mummy, that smokers are neurotic, dependent individuals unable to stand on their own feet without the aid of a symbol of maternal protection, while non-smokers are strong, independent, self-reliant types I am sure such an approach would have much more success than exploitation of the fear of cancer

Wednesbury,
Staffs

H B BAKER

THE ROYAL COMMISSION'S REPORT

SIR,—Your excellent leading article last week on the report of the Royal Commission states correctly that the recommendations on pay for house-officers are higher than the recommendations suggested by the British Medical Association This is true, but to complete the story you should also mention that the Commission's rates for house-officers are lower than those suggested by the Medical Practitioners' Union

Originally the B M A proposed a flat 24% (later 29%) for all grades In its evidence on the remuneration of hospital medical staff submitted to the Royal Commission in April, 1958, the M P U drew attention to the plight of junior hospital medical staff and the Spens recommendation that " intending specialists should not be called upon to pass through a period of comparative penury " This was one of the factors that led the B M A to raise the amounts suggested for registrars and house-officers The M P U submitted the same figures for consultants as those suggested by the B M A, but for registrars and particularly house-officers they were higher In this respect the Royal Commission has suggested figures which are somewhere in between

I think that it can be fairly said that the Medical Practitioners' Union has done a service to the whole profession by drawing the attention of the Royal Commission to this anomaly and with very excellent results The B M A has for the first time departed from its usual practice of serving only the vested interests of the part-time consultants It is to be hoped that, in the discussions which lie ahead, concern for the problems of the junior grades will be maintained

Bushey, Herts

P WATNEY ROE

LEISHMANIASIS ACQUIRED BY CONTAGION

SIR,—I was very interested to read Professor Symmers' paper of Jan 16, in which he states that it is remarkable that the woman's lesion took the form of an oriental sore typical of infection by *Leishmania tropica*, whereas her husband's disease was of the visceral type associated with infection by *L donovani*

It has been shown [1] that the East African strain of *L donovani* is very dermatotropic in that a primary skin lesion precedes the visceral infection. There is a latent period of commonly four to six months during which time only a skin lesion can be found. It is possible in the case described by Professor Symmers that, had the vulval lesion been allowed to continue untreated, visceral spread would have occurred and the woman would have developed kala-azar, or the nodule would have faded spontaneously as can happen in a smaller proportion of cases, without visceral spread. *The husband* was infected, during the early part of the East African campaign, in the Sudan Ethiopian area, where kala-azar infection is common and of the same type as is found in East Africa In East African kala-azar parasites are found in the normal skin in up to 11% of cases, so that infection by direct contact could have occurred in this way

King George VI Hospital
Nairobi

P E C MANSON-BAHR

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[1] Manson-Bahr, P E C *Trans R Soc Trop Med Hyg* 1959, 53 127

MEDICAL NEEDS OF INDIA

SIR,—I have read with great interest your leader Jan 30, 1960, and I should like to comment on some the points

India is trying through its five-year plans to raise th standard of living of its people This is, at present, extreme low, for the average income is less than £23 per head p annum, of which food consumption alone takes 60–70% I the first five-year plan (1951–52 to 1955–56) expenditure agriculture, community development, flood control, &c formed 32 1% of the total as against 5 9% on health Th provision is 20 9% on the former and 5 7% on the latter the second five-year plan (1956–57 to 1960–61) The expenditure on industries, mining, transport, communication, an power, which had the major share, formed 42 3% and 53 3 of the total expenditure in the two plans The total outl of the first and second plans were Rs 23,500 million an Rs 48,000 million respectively The national income increase by 18% in the first five-year plan and it is expected that it wi increase by about the same proportion in the second five-ye plan.

President Rajendra Prasad, when inaugurating the budge session of Parliament on Feb 8, 1960, said that the object o the third five-year plan, the preparation of which was makin good progress, would be to double the national income, takin 1950–51 as the basic level Greater attention would be paid t agricultural production and heavy machine building as wel as to development of basic resources like steel and power Th progress, though not spectacular, is steady and encouraging

On the agricultural front the results have not been encouraging The area of cultivated land per caput was 1 09 acres i 1891, 1 11 acres in 1921, and 0 84 acre in 1951—i e, nearly one-fourth less in 1951 than in 1921 With the present effort agricultural production in the second five-year plan has bee averaging a 3 5% annual increase India will require 110 million tons of food grains a year by 1965–66 when the population is expected to be 480 million, and she will have a shortage of 28 million tons of food grains if the present rate of production continues *During the past ten years India has been* importing, on the average, 2 5 million tons of food grains a year, at a cost of nearly Rs 1000 million

Probably no single factor is so important for the future progress of India as the solution of its sudden increase in population For India this has become the basic problem, for on its solution and balanced achievement depend all future progress Control of famines and epidemics, and the provision of maternity and child-welfare services, are lowering mortality and increasing the span of life

The expectation of life at birth in India in 1921–30 was 26 89 years, in 1941–50 it rose to 32 years, but in 1951–60 *it is* expected to be about 42 years, a gain of 10 years during *the present decade* India's population between *1891 and 1920*, when the natural checks were operating, increased by 12 million only, but between *1921 and 1950 it increased by* 110 million.

It is estimated that India's population, which was 357 million in 1951, will have expanded to 431 million in 1961, and at present the rate of increase is 2% per annum as against 1 3% *per annum in* 1941–50 Medical men may be blamed for bringing about this accelerated rhythm, but no-one can deny that medicine must serve society by conquering killing diseases, preventing epidemics, promoting and restoring health, and prolonging life so that it may be lived and enjoyed to the full But large families and disease may be responsible both *for high* morbidity and mortality, and population pressures and good health do not go together in countries with a low econom Too often Indian women alternate between gestation and *lactation* until their *premature death* The application of scientific medicine to improve the health of the people *in* underdeveloped countries aggravates the population problem, and as science can be used to reduce deaths it should also be used to reduce births

Government of India realises this fact fully, and the an Planning Commission clearly states in the second five-ear plan that "The problem of regulating India's population om the dual standpoint of size and quality is of the utmost nportance to national welfare and national planning" The overnment, therefore, is actively supporting a family planing programme and is giving it high priority A provision of early Rs 50 million has been made for this in the second lan, and 300 urban and 2000 rural clinics are being set up by the end of 1959 there were 1147 clinics of which 712 were n the rural areas)

The Census Commissioner to the Government of India, in is report on the 1951 census, laid down a national policy by hich India could attain a stationary population. This should e done by avoiding "improvident maternity"—defined as hildbirth in a mother who has already given birth to three or ore children, of whom one at least is alive In order to chieve this, the people, 83% of whom live in more than 00,000 villages in India, with no privacy or toilet facilities of ny kind, and who are mostly illiterate and ignorant, should have suitable and cheap means of contraception at their disposal. That is the biggest hurdle yet to be crossed in the way of family planning, and it needs serious thought and investigation by the demographers, medical men, and scientists In my opinion, coitus interruptus appears for the present to offer itself as the most practicable method for mass adoption. Oral contraceptives which would be acceptable may take a few decades of experimentation before they can be recommended for mass adoption.

All this, Sir, may seem far removed from the subject of your leading article, but it is only fair to pay due consideration to the background against which the medical needs of India must be assessed We, in this country, are trying to achieve results which "Western" countries have only enjoyed after perhaps a hundred and fifty years of intensive efforts We cannot hope, nor do we want, to imitate all aspects of Western medicine, for our way of life is, and must remain, different We do, indeed, welcome people who are prepared to come and work with us provided that they will stay sufficiently long to learn and understand the customs and habits of the country

May I make one further comment, on your criticisms of the administrative framework While it is true that this medical college is unique in India in that it is directly under the University, which is an autonomous body, all senior academic posts in medical colleges are, so far as I am aware, filled, like my own, after open advertisement and interview by a University Selection Board or the State Public Service Commission on which there are independent assessors or experts

Department of Social and
Preventive Medicine,
King George's Medical College,
Lucknow University,
Lucknow, India

B G PRASAD

AMINE IN SEARCH OF A FUNCTION

SIR,—Your annotation of Dec. 12 with this title seems to imply that this agent is also in search of a name It is variously known as 5-hydroxytryptamine, 5-OH-T, 5-HT (the jazzy variant, 5-HOT has been wisely overlooked), serotonin and, in an early guise, enteramine

The chemical names are specific to a degree but, since they begin with the strident word "five", cacaphonous Trivial names may properly describe functions, among these, our term "serotonin" alludes both to one of the source materials and to this amine's major effect on smooth muscle, while Erspamer's "enteramine" characterises a single, possibly physiological function. However, few are so humble as to wish to rest even their primitive central nervous activities on so gutty a base as enteramine (The pun is intentional.) Hence, the term "serotonin" seems both defensible and useful Lastly, it is a pity to burden medical letters, bemuse indexers, and confuse students with increasing numbers of names for the same thing, or further to separate the English and American languages, now divided on such terms as "elevator" and "lift", "braces" and "suspenders", by adding this particular

There may be another solution C of E, Paleyian theology directs us to the view that anything as widely distributed in Nature and active in so many ways must have major significance in the Order of the Universe Since we cannot yet define this in any unitary way, perhaps an alternative to "serotonin"—viz, "confusotonin", once proposed in jest—deserves more serious consideration by some appropriate reference committee

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A C CORCORAN

TREATMENT OF ADVANCED CARCINOMA OF THE BREAST

SIR,—In their valuable contribution of Jan 16 Dr Brinkley and Dr Pillers make the dogmatic statement that "operation is necessary because X-ray castration does not completely stop ovarian function" I am sure that many would be grateful to know the evidence for this statement

In the breast clinic in this hospital the œstrogen content of vaginal smears has been seen to fall dramatically following radiation castration, and in other cases no appreciable alteration in œstrogen content has occurred following surgical castration. In these latter cases other sources of œstrogenic function are evidently still active and one would not conclude that the ovarian function had not been completely stopped by the operation. There is also abundant clinical evidence of regression of breast carcinoma following radiotherapeutic castration.

In many instances operation is undoubtedly to be preferred. When a rapid response is required in a patient with fulminating and rapidly progressing disease, the effect of surgical castration is more dramatic and more rapid than if ovarian function is affected by external radiation. On the other hand, it is our experience that the menopausal symptoms are less severe if X-ray castration is employed. It would, therefore, be unfortunate if the impression were gained that oophorectomy is always to be preferred to radiation castration.

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Baltimore.

R J DICKSON

IMMUNE TOLERANCE IN MOTHER AND FŒTUS

SIR,—It is difficult to understand why the fœtus, which achieves antigenic competence in utero, is not rejected by the mother by immune phenomena much in the manner that a primary skin homograft would be Many explanations have been proposed for this surprising manifestation of immune tolerance but none has yet received general acceptance Dr Gordon's[1] intriguing hypothesis (Jan 9), with which I cannot agree, prompts me to put forward my own theory which at the present time is based on ample contributory evidence and is strongly supported by preliminary experimental observations

Although Woodruff[2] has postulated that the placenta may protect the fœtus by acting as a millipore filter, no account has been taken of the antigenic action of the placenta itself, which is, after all, of fœtal genetic origin The syncytiotrophoblast may well play an important role in this respect, for this unique tissue is not only the first part of the embryo to come into contact with maternal tissue at implantation but also remains the sole fœtal tissue that ever associates with maternal cells The syncytiotrophoblast possesses many interesting features apart from its syncytial character The nuclei are in general smaller than those of the adjacent cytotrophoblast and, although rapidly multiplying especially during the early stages of development of the placenta, are never seen in mitosis Syncytiotrophoblast invades the endometrium with apparent impunity, eliciting no tissue reaction whatsoever Recently, careful search by Sohval and his colleagues[3] has failed to demonstrate the presence of the Barr nuclear chromatin body in the nuclei of these cells in the placentas of female fœtuses, although it has been identified in every other cell type of such placentas

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[1] Gordon I *Nature, Lond* 1960, 185, 118, *Lancet*, 1949 i, 807

[2] Woodruff, M F A *Proc roy Soc* B, 1958, 148, 68

These considerations lead me to suggest that the nuclei of the syncytiotrophoblast are haploid, possibly possessing only the maternal chromosome complement and thus resulting in a tissue genetically acceptable to both mother and fœtus

Owing to the absence of mitoses it is impossible to test this hypothesis directly by chromosome counts, but the recently developed technique of Feulgen microspectrophotometry for the determination of the D N A content of individual nuclei provides a useful method for attacking this problem Comparative studies of D N A content by this method, chemical estimations, and direct chromosome counts provide excellent agreement and it is established that this is a reliable method to determine the ploidy of any given nucleus[4]

Preliminary results from study of material at present available indicate that the syncytiotrophoblast of immature placentas contains a large number of haploid nuclei Tissue from therapeutic abortions, mature placentas, hydatidiform moles, and choriocarcinomas is now being collected for examination of nuclear D N A content by microspectrophotometry

A full discussion of the implications of this finding and the possible mechanisms involved is presented elsewhere[5]

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MICHAEL GALTON

PAINLESS SKIN BIOPSY

SIR,—Chromosomal studies in man are usually conducted on cultures derived from marrow, blood, or skin Skin has the advantage that it travels well, leads to good preparations without squashing, and is known to be capable of being maintained in culture for many months, but it is often regarded as difficult to acquire

I have found, after taking many skin biopsies from myself, a very simple and painless method which requires little equipment, no local anæsthesia, no aftercare, leaves no scar, and yet provides adequate tissue for establishing culture The term painless may seem exaggerated, but, with practice, this can be achieved Even if inexpertly but carefully performed it is likely to be less painful than venepucture, while failure is impossible

A piece of skin is made lax by gently squeezing between the finger and thumb, and a ridge of this skin is trapped between the shafts of a pair of forceps The shafts should be rounded in cross-section Toothed iris forceps are suitable if care is taken to keep the teeth clear of the skin

The hump which bulges through the gap should be about 1 mm high, 1 mm wide, and 5 mm long, and should not extend as far as the points of the forceps After thirty seconds of gentle pressure the skin becomes pale and opalescent and is found to be completely insensitive The protruding skin is removed by sliding a dry scapel or razor blade along the forceps away from the points For cell culture, skin cleaning should be by some completely volatile fluid, as ether Razor blades are convenient as they may be sterilised in an oven while still wrapped The few drops of blood are adequate for 2–10 slides The resulting wound is flame-shaped, and heals over without contraction, being very shallow, infection is unlikely

The area chosen seems immaterial The iliac crest region is convenient in children and babies, and skin may be taken during sleep

Sections of the biopsy show approximately equal numbers of mesodermal and epithelial cells The specimen is adequate for sexing, although only rarely will this be preferable to the buccal mucosa or the white blood-cells Although small, the biopsy may also be of use in those skin disorders in which relatively rough treatment will not confuse the histology

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Population Genetics Research Unit,
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J H EDWARDS

CLOSED WOUND DRAINAGE

SIR,—Primary closure of surgical wounds is the ideal and although it is sometimes impossible, there is no longer a place for open drainage of wounds or drainage into dressings Primary closure may be prevented by

The need to drain a duct or a secreting hollow viscus
Where a secreting gland has been transected
The desirability of obliterating a tissue space by the removal of blood, or accumulated tissue fluid
The drainage of a productive abscess
The drainage of a site of infection where localisation has not occurred or where a fistula may form

Closed drainage with or without suction has many advantages infection is reduced, wound healing is expedited, the discomfort of soaked dressings is avoided early changing of dressings is unnecessary, and the cost of treatment is less[1]

The methods used in the surgical department of this general hospital in recent years are

Water-seal drainage with or without suction
Closed drainage for bladder cases
A Penrose drain or pack
Tube drainage with a plastic suction bottle

Thoracotomy demands water-seal drainage, sometimes with suction, and closed drainage in such a case is a well-established method In our practice when any form of suction is applied to the chest, a "three-tube" bottle providing a safety valve is always fitted to the system between the source of suction and the standard water-seal bottle

Closed drainage for bladder cases is also standard Before the operation we use the Gibbon's plastic catheter and bottle[2] After operation whatever catheter is employed, whether urethral or suprapublic, is connected to a Tudor Edwards empyema bottle The neck of this bottle is sealed with a rubber cork, and the air vent is occupied by a thistle-shaped steel cup containing formalin tablets, loosely wrapped in gauze[3]

In some cases tube drainage may be unsatisfactory—for example, in a case of appendicitis with perforation, especially if the appendix is retrocæcal or requiring much dissection It may be unsatisfactory because, though it establishes drainage from one loculus, other pockets of infection may develop in the pelvis or elsewhere Provided the appendix has been removed and the appendix base securely closed—that is, if the source of pus formation has been removed and the risk of fistula formation has been minimised—it is better, we feel, to use the Penrose drain. *This prevents* further bleeding and accumulation of fluid by exerting pressure on the raw area, and at the same time it promotes healing and forms a track if infection or fistula formation should ensue This drain is left undisturbed for five to six days

If there has been much bleeding, or fluid is likely to accumulate, a drainage tube and suction will not only remove the fluid but also air, and thus reduce the size of any potential cavity (e g , after mastectomy, retropubic dissection, neck dissection renal surgery, and the removal of large space-occupying tumours) If a secreting gland has been transected, as in partial thyroidectomy, there is a further indication for drainage vacuation of an abscess leaves behind a pyogenic cavity which ontinues to produce infected material Closed drainage revents the dissemination of infection, at the same time eeping the cavity empty and reducing its size

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[3] Sohval A R, Gaines J A Strauss L *Ann N Y Acad Sci* 1959 75 905
[4] Leuchtenberger C in General Cytochemical Methods (edited by J F Danielli) New York 1959
[5] Galton M *Nature Lond* (in the press)

[1] Sheppard M D *Lancet* 1952 i 1171
[2] Crosbie Ross J Gibbon N O K Damanski M *ibid* 1957 ii 520
[3] Riches, E W *Practitioner* 1952 169 3[illegible]

In this group of cases we use closed drainage with suction, mploying polyethylene bottles No originality is claimed for he method but it has proved so successful that we feel its dvantages should be more widely known For the drainage ube we use a plain rubber or portex catheter of approximately ize 10 (English gauge) To this is attached a light polyethylene ottle which has a screw-on cap with a tapering nozzle, also ade of polyethylene The walls of the bottle are lightly compressed as the nozzle is inserted into the end of the catheter, so hat a low negative pressure is created, sufficient to draw pus, lood, or serum from the far end of the catheter into the bottle

The advantages of this method are numerous

Dressings remain clean and need not be changed in the early postoperative days when the wound is most tender Economy in dressing materials and nursing time is considerable and bacterial dissemination is reduced

It is a simple matter to check at any time that the system is functioning efficiently

One has a sterile and immediately visual method of assessing when the drain might have fully served its purpose and be withdrawn without any need to disturb the dressing

The quantity of drainage is measurable, and can be recorded on the patient's fluid chart when appreciable in amount

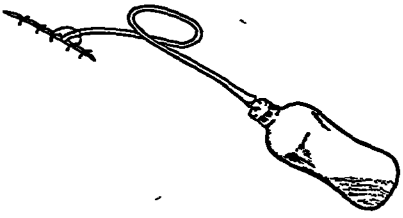
The bottles are made of low density polyethylene and are very light to handle

They are cheap and can be used many times

This suction drain operates continuously and silently with very little supervision

The patient can be fully ambulant while suction is maintained

Attention to the following practical points is important The drain tubing must be firm enough so that it will not collapse with the negative pressure For this reason we use a Jacques or Harris catheter with several extra holes cut The fluted proximal end allows easier insertion of the nozzle and can be cut to the size required for a secure fit The catheter is held by a double suture inserted close on each side (see figure) and it is important to avoid puncturing the catheter with the needle



It is essential to avoid over-compression of the bottle especially after repeated use, otherwise it will become kinked and will not re-expand The bottle interior is sterilised by filling with a 1 in 20 solution of carbolic and there has been no sepsis attributable to the use of this method. Two sizes of bottle (4 oz. and 10 oz) have been used, the smaller size being suitable for most cases Experiment has shown that both sizes of bottle can draw up a column of water 4 mm in diameter to a height of 100 cm. After repeated use the polyethylene tends to harden and the suction power is reduced This negative pressure has not given rise to any complications in practice and compares favourably with the use of many electric pumps which may go on building up an ever-increasing negative pressure Moreover, they effectively immobilise the patient and may cause considerable annoyance if the pump is noisy The polyethylene bottles, on the other hand, are eminently portable and silent

Despite the limited calibre of the catheter and dispenser spout, there has been no tendency to blockage We are at present experimenting with nozzle fittings of different shape and size The screw-on top is being retained, however, because of the access it allows for cleaning

I am grateful to Mr J Hutchison for much helpful criticism and advice, and to Mr P S Waldie, A R.P S for the diagram

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Glasgow

F T CROSSLING

BONE-MARROW GRAFTS IN LEUKÆMIA

SIR,—In the discussion of the use of autologous marrow grafts in your leading article of Jan 23 mention is made of three of our cases of leukæmia in which we employed total-body irradiation and infusion with autologous marrow obtained during a remission.[1] It might be of interest to add the follow-up of the patient in whom a remission was achieved by this procedure

The patient, a 2-year-old girl, remained well until the 84th day after irradiation, when the liver, spleen, and lymph-nodes were observed to be enlarged, and a bone-marrow aspirate showed recurrence of leukæmia. A-methopterin therapy, to which she had become refractory before irradiation, was reinstituted, with some regression in the size of the lymph-nodes and a fall in the white-cell count However, she died while being given a blood-transfusion 102 days after irradiation. Postmortem examination showed leukæmic involvement of the liver, spleen, lymph-nodes, bone-marrow, and kidneys Several walled-off splenic abscesses caused by *Staphylococcus aureus* were present. In addition to involvement by leukæmic infiltrates the lymph-nodes showed scattered follicles, and the stomach and intestines contained many prominent lymphoid follicles with germinal centres

Although a remission was obtained in this one case, we believe that further investigation is necessary to determine whether bone-marrow grafts are of practical value in the treatment of leukæmia.

LEONARD ATKINS
JOSEPH J MCGOVERN
PAUL S RUSSELL
EDWARD W WEBSTER

Massachusetts General Hospital,
Boston

DISCHARGE FROM A HOSPITAL VACUUM SUCTION SYSTEM

SIR,—A piped vacuum system is being installed in New Guy's House, which is now under construction This department was asked to advise whether there was any danger from the exhaust from such a system, which might collect pathogenic organisms, particularly antibiotic-resistant staphylococci, and discharge them into the atmosphere As inquiry revealed no information on this matter, it was decided to investigate an existing vacuum system That at the Royal Marsden Hospital was selected

It was installed in 1948 and consists of suction points, in three operating-theatres, a reservoir tank, and a pump in the basement with a discharge pipe to a basement yard. The vacuum is maintained between 15 and 25 in. of mercury Through the cooperation of the Royal Marsden Hospital and British Oxygen Gases Ltd, the following investigations were carried out

(1) Three sections of pipe were cut out—near a suction point, in the main vacuum line from the theatre floor, and just before the tank The inside of each pipe was found to be dry and macroscopically clean Swabs were taken from these three sites and from the inside of the tank Direct plating produced no growth, and enrichment in broth grew *Staphylococcus albus* and diphtheroids from two swabs only

(2) The effluent air was sampled by passing it through a plug of sterile alginate wool of approximately 1 cm diameter which was then dissolved in a 1% sodium hexametaphosphate solution containing 10% horse serum The resulting solution was cultured Two tests were made on different days in which 150 and 200 litres of air (as measured by a gas meter) respectively were pumped On the first occasion the vacuum was broken at the entrance to the tank, no organisms were recovered On the second occasion the vacuum was broken at a suction point in a theatre so that air was drawn through most of the system *Staph albus* was isolated, on enrichment only

Quantitative control tests using *Staph aureus* showed that the solvent used was not significantly inhibitory

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[1] *New Engl J Med* 1959, 260 675

(3) The tank was opened by British Oxygen Gases Ltd , and was found to be surprisingly clean No fluid was present, but there was evidence that there had been a pool of liquid at some time, as there was a "high water mark" of encrusted deposit When this was examined under the microscope no microorganisms could be seen and it yielded only a micrococcus and an aerobic sporebearing organism, separately from two enrichment cultures

Thus it was not possible to isolate any pathogenic organisms from the system examined, and non-pathogens could be recovered only by enrichment methods The difficulties of using an aseptic technique in the circumstances described do not rule out the possibility of chance contamination The low level of contamination was a little surprising, but it may be due to the dry conditions inside the vaccum system, the lack of nutrients, and possibly the fact that much of the piping was of copper "Heat-sterilisation" of air has been achieved by adiabatic compression in reciprocating compressors,[1] and the pump in the system here described may have been acting in this way

The significance of one set of tests on a single vacuum system is doubtful, and different results might be obtained in a hospital where many septic cases were treated, but it is thought that the information obtained is of sufficient interest to be worth reporting

Department of Bacteriology,
Guy's Hospital Medical School,
London, S E 1
J C KELSEY

DEPRESSION AND IMIPRAMINE

SIR,—Undue sweating has been described as a side-effect of imipramine ('Tofranil') It appears to me, after a certain amount of experience with this drug and its effects on endogenous depression, that those patients who respond well tend to complain of undue sweating in the early stage of their treatment, whereas those who do not respond do not notice any such sweating

Can it be that we have here a sign of prognostic import which might be useful in determining whether it is worth persevering with this drug in certain cases?

I should be extremely interested to hear from your readers who have perhaps greater experience with imipramine whether they have noticed any such correlation between excessive sweating and good prognosis

London, W 1
R CEDRIC SIMPSON

CHROMOSOME COMPLEMENT IN A MONGOLOID MOTHER, HER CHILD, AND THE CHILD'S FATHER

SIR,—Of the three human diseases due to a chromosome abnormality—mongolism, Klinefelter's syndrome, and Turner's syndrome—mongolism is the only one in which instances of fertility have so far been reported To our knowledge there are six reports of women with mongolism having had a child which was adequately described[2–7] Three of the children were mongols[3 6 7] It is of obvious interest to obtain information on the karyotype of these fertile mongoloid patients and their offspring Levan and Hsu[8] have briefly mentioned the result of such a study in a mongoloid mother whose son had a normal chromosome complement

We have investigated a mongoloid mother, her son, and the reputed father by determining the chromosome complement of cells cultivated in vitro A detailed description of these individuals was given by Forssman and Thysell[4] Bone-marrow cells were cultivated according to a technique described by Fraccaro et al[9] The 35-year-old mother had 47 chromosomes The apparently normal 5-year-old boy and the father, a 59 year-old blind man with epilepsy, had normal karyotypes of 46 chromosomes

Further details will be published elsewhere

Pediatric and Psychiatric Departments
and Institute of Histology,
University of Gothenburg, Sweden
O LEHMANN
H FORSSMAN

AUTOGENOUS VACCINES AND THE COMMON COLD

SIR,—I must apologise for writing you a long letter on this subject, but the trial reported in your issue of Feb 13 requires some strong comments This R A F trial, although using the same vaccine, was conducted on essentially different lines from that reported by me in 1958 The points of difference are

(1) Last paragraph of preamble (p 358) "The vaccines were prepared in the same way as Ritchie had prepared his, but the dosage schedule was modified, as weekly injections would not be welcomed by healthy men and would be difficult to arrange on an operational flying station" The variation in the dosage schedule invalidated the whole R A F trial from the beginning Our trial, which, it must be noted, really lasted for over 25 years, depended on the maintenance of immunity over a period, by regular weekly injections, not by a mere token series of three in October plus one single injection in January As I pointed out at the time, that system of dosage is completely subminimal and useless, rendering their results quite valueless They can in no way be compared with the results I reported in 1958

(2) The next sentence in the same paragraph on p 358 reads "Furthermore there seemed to be no theoretical reason why weekly injections should produce a better immunological response than a more usual course" There is no "usual course" in a prophylactic cold vaccine of this kind No-one has tried the procedure but myself, and I have found from experience that the only course is one of weekly injections throughout the part of the year concerned If the R A F found this impracticable they should not have tried a make-shift substitute of their own, much less have attempted to compare it as if it were on the same lines as previous work. The phrase "usual course" suggests a complete confusion of mind between coccal vaccines and those prepared for the zymotic diseases, such as typhoid, where one attack confers lifelong immunity, more or less Anyone who has used *Staphylococcus aureus* vaccines, for example, over a period of years with 100% success, as I have, knows that these coccal vaccines must be maintained over a considerable period to get the result That is the "usual course" for a coccal vaccine, not a few haphazard doses at intervals

Table III (p 360) has an interesting comment, that volunteers who were vaccinated did not lose less flying-time "except to a small degree during the first 2 weeks after inoculation with autogenous vaccine" In other words, during that period the vaccine was beginning to work, but with the cessation of regular injections the effect was lost Had these been carried on the results might well have been greatly different The comment on table IV shows a similar trend

"There was, however, an interesting reduction in the incidence of illness in the autogenous-vaccine group in the period when it might be expected, between the 3rd and 6th weeks after inoculation" This fits in with my comment in the previous paragraph and again suggests that the vaccine was beginning to work

It is also observed that "a vaccine designed to prevent secondary bacterial infection would be expected to reduce the severity of illnesses rather than their incidence" That is frankly nonsense Vaccines of this kind are intended to promote resistance and therefore to reduce incidence Once resistance is overcome, the severity of an illness depends

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1 Sykes, G , Carter D V *J appl Bact* 1954 17, 286
2 Sawyer, J M *Amer J ment Def* 1949 54 204
3 Lelong M et al *Arch franç Pédiat* 1949 6, 231
4 Forssman H , Thysell T *Amer J ment Defic* 1957, 62, 500
5 Schlaug R *Acta genet* 1957, 7, 533
6 Rehn A T , Thomas E *Amer J ment Defic* 1957, 62 496
7 Stiles K A Proceedings of X International Congress of Genetics, Montreal 1958 vol 2 p 276
8 Levan A Hsu, T C *Hereditas* 1959 45, 665
9 Fraccaro M , Kaijser, K , Lindsten J *Ann hum Genet* (in the press

chiefly on the virulence of the infecting agent, and an infection powerful enough to overcome an enhanced resistance will necessarily be severe Even typhoid, if I may quote a zymotic vaccine as a parallel in this case, is not necessarily milder in the vaccinated when it occurs

In short, this R A F test proves nothing except that a thing is not worth doing unless it is well done The only sentence with which one can wholeheartedly agree is the last in the paragraph under Comments, that " autogenous bacterial vaccines, perhaps in greater dosage, may therefore merit further investigation among less healthy persons " Even here the word " perhaps " should be replaced by " certainly "

Birkenhead J MORRISON RITCHIE

PERTHES' DISEASE

SIR,—You annotation of Feb 16 refers to my finding [1] that in cases of Perthes' disease with partial involvement of the upper femoral epiphysis the prognosis was better than in those cases in which the whole epiphysis was involved A study of my figures will show that this is so, when variations in age and sex have been eliminated The prognosis appears to become much worse if the child is eight years old or over at the time of diagnosis

In regard to the long-term end results neither the figures of Ratliff [2] or of Professor Trueta [3] absolve the orthopædic surgeon from adopting full treatment immediately

Often in the young child the disease damages the whole epiphysis or a large anterior segment of the head Traction in recumbency until reconstruction begins, followed by the wearing of a patten-ended calliper, gives good results in these hips Mild cases do not require recumbency In older children treatment does not seem to affect the result

The Royal Hospital,
Wolverhampton J A O'GARRA

NORADRENALINE EXCRETION IN INDIAN SUBJECTS

SIR,—Floyer [4] described a simple biological test for an approximate estimation of urinary noradrenaline Urine was injected intravenously into an anæsthetised rat and the rise in blood-pressure was measured This simple technique has been used to estimate the noradrenaline content in the 24-hour urine samples in eighteen Indian subjects (fourteen hypertensives and four controls)

A slight modification in the anæsthesia was that 0 6 ml per 100 g body-weight of 25% urethane was injected intraperitoneally, and no further subcutaneous injections of urethane were given to prolong the anæsthesia for several hours

The results indicated that the excretion of noradrenaline in Indian subjects is about the same as that described elsewhere [5] In thirteen of the subjects the noradrenaline content was 65 μg or less in 24 hours Robson and Keele [6] stated that the normal concentration of catecholamines in urine is 5–15 μg per 100 ml urine In our results seven subjects had a noradrenaline excretion equivalent to 1 5 μg per 100 ml or less, while four excreted less than 4 μg per 100 ml urine It is possible that values less than 5 μg noradrenaline per 100 ml urine are normal for Indian subjects

The method described by Floyer [4] is a simple and convenient way of estimating the noradrenaline content of the urine and screening cases for phæochromocytoma The noradrenaline content in 24-hour urine in Indian subjects appears to be nearly of the same order as in other subjects described previously

I should like to thank G S Ahluwalia for his excellent technical assistance

Department of Pharmacology,
All India Institute
of Medical Sciences,
New Delhi RANJIT ROY CHAUDHURY

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[1] O Garra J A J Bone Jt Surg 1959, 41B 465
[2] Ratliff, A H C ibid 1956, 38B 498
[3] Trueta, J Lancet, 1960 i 383
[4] Floyer M A Lancet, 1958, ii 1154
[5] Von Euler, U S Noradrenaline American Lecture Series, no 261 Springfield Ill 1955
[6] Robson J M, Keele, C A Recent Advances in Pharmacology London, 1956

PREVENTION AND TREATMENT OF BEDSORES BY SILICONE CREAM

SIR,—I should like to add a note to the report of Dr Roberts (Jan 30)

During the past two years, I have treated 80 patients in this hospital—the majority of whom were incontinent—with the creams I and II made and kindly supplied by Messrs Ward Blenkinsop Cream I containing dienœstrol is the more effective and is excellent for the prevention of sores when the skin becomes reddened at pressure points, for superficial bedsores, and for accelerating healing when deeper sores are beginning to fill in

I did not, however, find it adequate as the sole dressing in treating deep bedsores, for which I still follow my previously published routine of changing the application used every three days until healing is initiated

Royal Hospital and Home for Incurables,
Putney, London, S W 15 V KENDALL

RECESSION OF EXOPHTHALMOS AFTER MASSIVE DOSES OF RESERPINE

SIR,—Sir Russell Brain [1] emphasised that, in sera from exophthalmic cases, a hypophyseal substance similar to T S H is present Dobyns and Wilson [2] produced exophthalmos in the minnow by injecting the serum of patients with severe or progressive exophthalmos, and their findings suggested some correlation between the degree of response in the fish and the stage and severity of the patients' exophthalmos Barraquer and Canadell [3] made similar observations We should like to describe a patient with exophthalmos who reacted favourably to reserpine

A woman of 45 was admitted to hospital in 1959 because of paranoic psychosis accompanied by disorientation, amnesia, depression, and suicidal drive She had undergone thyroidectomy in 1944 because of Graves' disease, and a partial adrenalectomy in 1951 for phæochromocytoma Apart from the psychotic disturbances, severe diencephalic and endocrine insufficiency syndromes had developed in the patient The most troublesome symptom was severe exophthalmos For six months she had no menstrual cycle, apparently because of incipient menopause

Reserpine (10 mg daily) was injected intramuscularly Definite improvement in the exophthalmos was noticed after five days, whereupon the reserpine was discontinued Within a week, the exophthalmos recurred as badly as before Reserpine was renewed, and by the eighteenth day the exophthalmos was hardly noticeable

Urinary F S H was continuously assayed during this period, decreasing from 50 rat units per litre before treatment to less than 25 later This improvement in the exophthalmos and the endocrine symptoms did not, however, produce any obvious change in the psychosis, and disorientation, amnesia, and depression persisted

We have been able to show that reserpine depresses some pituitary tropins, especially F S H , apparently via the hypothalamus, and we therefore assume that in the patient whose urinary F S H levels were high, reserpine depressed the pituitary secretion of both the exophthalmo-genic factor and the gonadotrophic factor The question is still open whether this case is a singular one and reacted to reserpine because it was a hypophyseal-diencephalic exophthalmos, as described by Zondek,[4] or whether every exophthalmos is liable to recede after high doses of reserpine

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[1] Brain W R Lancet, 1959, i 109
[2] Dobyns, B M Wilson L A J clin Endocrin 1954 14 1393
[3] Barraquer, J , Canadell, J M Rev esp Oto-neuro-oftal 1955, 14, 274

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Hebrew University-Hadassah Medical School
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TREATMENT OF CEREBRAL FAT-EMBOLISM

SIR,—Reading the article[5] by Dr Harnett and his colleagues, I was surprised at the remark, " Attempts at specific treatment have not been very successful " I do not agree and I wish to draw attention to two articles published during recent years

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Amsterdam A G J VAN SONDEREN

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In this country the Ministry of Health's weekly influenza statement for the week ended Feb 13 said there had been no laboratory evidence of influenza virus A or B, nor other evidence of the prevalence of influenza

Medicine and the Law

A Partner's Notes

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Robinson *v* Robinson—*Probate, Divorce, & Admiralty Division* Phillimore, *J* Feb 18, 1960 Counsel and solicitors John Alliott (Rootes & Alliott, of Folkestone)

D R ELLISON
Barrister at-Law

Parliament

Social Workers and Their Training

ON Feb 17 the EARL OF FEVERSHAM drew attention to the Younghusband report[1] and sought the Government's reactions to its recommendations His own were favourable, for he believed that lack of training and status had lost the social services many potential recruits in the last fourteen years The local authorities' growing responsibilities under the welfare and health Acts made the recruitment of more social workers a matter of urgency He was particularly impressed by the need for trained mental-welfare officers, 40% of the present officers were due to retire within the next ten years

Lord AMULREE felt that the training proposed in the report was a trifle on the theoretical side He was also uneasy about the report's tendency to regard the health and welfare departments as separate entities In his view there was some sort of medical aspect to most welfare and social work and he would like to see the welfare and health departments, if not combined, which would be ideal, at least working closely together, with the medical officer of health a member of the two committees or having both working under his care

Baroness WOOTTON OF ABINGER thought that some of the report's recommendations were not entirely realistic The grading of the workers and the classification of the cases seemed to her too tidy In practice people might be handed from one worker to another One of the besetting diseases of our community was a delight in professionalism for its own sake Another was a tendency to confuse the economic and psychological She would be the last to dispute that where there was a problem of mental health, psychological training was essential, and it was deplorable that so few of our mental-welfare workers had had that kind of training But she thought that interest in psychological problems sometimes led to failure to discriminate between a plain practical need—often lack of money—and a true mental or psychological difficulty In her view many of the problems with which the social worker had to deal were basically economic. People who had fallen into difficulties from lack of money should not be treated as though they were failures in personal or social functions, and she hoped that the Government would be cautious in the type of training which they provided for the modern social worker Might the report be made the occasion for fresh thinking about a new orientation for the role of the social worker in our society ?

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[4] Zondek, H Die Krankheiten der endokrinen Druesen, p 305 Basle, 1953
[5] Harnett R W F, Paterson J R S, Lowe, K G, Stewart, I M, Wyman J D *Lancet*, 1959, ii 762
[6] Sonderen A G J van *Ned T Geneesk* 1957, 101, 538
[7] Rappert L *Dtsch Z Chir* 1939, 250, 276, *Wien klin Wschr* 1953, 65 603
[8] Schmitter, H *Münch med Wschr* 1958, 43 1658

[1] *Lancet*, 1959, i, 974

Baroness SWANBOROUGH was worried about the suggestion in the report that people who were at present doing good work should have to submit to further training She welcomed the idea of a form of training but thought that the over-elaboration which came with an obsession for professionalism was a hazard. She agreed that there was infinite danger in assuming that because people were in financial need they must be handled by trained social workers Social welfare was a continuing process, and trained workers should have volunteers to continue the work at the local level. Voluntary service should be the mortar between the bricks of officialdom

Lord TAYLOR agreed that it would be better not to categorise too much in planning the future training of social workers, and he thought that perhaps the idea of the welfare assistant could go But everyone was agreed on the need for many more social workers The question remained would the Government pay the extra salaries which these people would have to get ?

The main message of the report, Lord ST OSWALD had found, was that social-work services needed more training and more manpower To him the two went hand in hand, for one of the incentives to recruitment would be training To this end the Younghusband Committee had made purposeful and detailed proposals The Government were grateful to the authors of the report and were now weighing, not only their advice, but the advice they had drawn from other quarters The recommendations must be considered in the light of local-authority views Equally, several departments, including the Ministry of Health, that of the Secretary of State for Scotland, the Home Office, the Ministry of Education and, last but not least, the Treasury were closely concerned. The local-authority associations and the main voluntary bodies had already expressed their general views It might be necessary now to obtain their views on specific details, but time would not be wasted

Welfare of Office Workers

THE Offices Bill was introduced as a private member's measure by Mr Richard Marsh on Dec. 11 Although the Government felt that it should not proceed, the second reading was carried[1] The Government have now signified their support by tabling a money resolution authorising an increase in the payments to local authorities to meet the cost of enforcing the measure

QUESTION TIME

Locum Tenens

Mr L A PAVITT asked the Minister of Health if he was aware of the inadequacy of the present arrangements to employ locum tenentes in general practice and the hospital services —Mr WALKER-SMITH replied I am aware that individual difficulties sometimes occur, but I am not clear that action by me would be appropriate Mr PAVITT In view of the fact that so many of these difficulties occur because of the time taken to solve these problems of locum tenentes, will the Minister give consideration to the introduction of a scheme for a local service, and further, will he consider the possibility of using the trainee assistants scheme in order to help in this respect ? For example, if the trainee were given two months at the end of his normal training period to enable him to obtain wider experience on a general basis and also in hospitals that would help Will he also consider the possibility of refresher courses for consultants and specialists, so that they may come down into the arena of family doctoring, which might be beneficial to them and help the general practitioner in solving his problem of locums ?—Mr WALKER-SMITH On the first of those three points, I doubt whether an organised service of the sort suggested would really meet the case because there are so many and varied personal factors involved in these matters On the second point, I should like to consider the suggestion The third point is very revolutionary in a professional service, and I think that, like Agag of old, I had better tread delicately -

Dr EDITH SUMMERSKILL While not asking the Minister to commit himself now, will he reconsider his first answer ? As he realises, the great majority of doctors today are employed by the State and find it very difficult to obtain a deputy in case of illness, in fact, there is no certainty that they can obtain a deputy This also applies during holidays We should at least equate doctors with Civil Servants so that deputies who can be relied upon are available. Perhaps the Minister will reconsider the whole matter ?—Mr WALKER-SMITH I am always ready to consider further these matters, but I was giving my impression as it now stands We should not exaggerate the difficulties about locums In particular, we have to remember that there has been a considerable increase in the number both of general practitioners and hospital doctors overall These difficulties have to be seen against that more satisfactory background

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Obituary

FRANK BARNES

M S Lond , LL D Birm , F R.C S

Mr Frank Barnes, consulting surgeon to the Birmingham General Hospital, had made many gifts to the United Birmingham Hospitals and the Medical School, and a ward in the Queen Elizabeth Hospital is dedicated to him. The postgraduate surgical travelling fellowship he endowed in 1944 has enabled young surgeons to widen their experience by working abroad More recently he gave generously towards the building of the new library at the Medical School which, in recognition of his own and the late Stanley Barnes' distinction and generosity, has been named the Barnes Library Mr Barnes was to have performed the opening ceremony last October but to everyone's sorrow he was too ill to do so He died on Feb 18 at the age of 90

He was born, lived, and worked in Birmingham all his life After qualifying from Mason College, Birmingham, in 1898, he took the degree of M B Lond. two years later He held many resident surgical appointments before being elected to the honorary staff of the Birmingham General Hospital in 1903 He was also consulting surgeon to the Birmingham and Midland Eye Hospital, the Hospital of St. Cross, Rugby, and the Sutton Coldfield Cottage Hospital, and for ten years he was on the staff of the Birmingham Orthopædic and Spinal Hospital (now the Royal Orthopædic Hospital) During the 1914–18 war he served in the R.A.M C

As a teacher he was lucid and orthodox and in the University was lecturer in anatomy and operative surgery He published little and he evaded high office and public recognition, but he served as president of the Midland Medical Society in 1930 In 1957 the University of Birmingham conferred on him the honorary degree of LL D

A G W writes

" Mr Barnes was a surgeon of outstanding ability, combining high diagnostic acumen with superb operative skill and dexterity and these qualities and his quiet, friendly, and unassuming personality made him one of the most sought after surgeons in the Midlands over many years He practised in the days before the increasing diversity and complexity of surgical techniques demanded narrow specialisation and he was essentially a general surgeon, but his major interests were abdominal surgery and neurosurgery He was one of the first surgeons in England to operate successfully on tumours of the spinal cord.

" Although they were not related, Mr Barnes and the late Stanley Barnes were close friends and they spent much of their leisure together fishing, playing golf at Moseley Golf Club, and bridge at the Clef Club Mr Barnes was also a keen genic factor and the gonadotrophic factor The question is still open whether this case is a singular one and reacted to reserpine because it was a hypophyseal-diencephalic exophthalmos, as described by Zondek,[4] or whether every exophthalmos is liable to recede after high doses of reserpine

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[1] See *Lancet*, 1959, ii, 1151

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The main message of the report, Lord ST OSWALD had found, was that social-work services needed more training and more manpower To him the two went hand in hand, for one of the incentives to recruitment would be training To this end the Younghusband Committee had made purposeful and detailed proposals The Government were grateful to the authors of the report and were now weighing, not only their advice, but the advice they had drawn from other quarters The recommendations must be considered in the light of local-authority views Equally, several departments, including the Ministry of Health, that of the Secretary of State for Scotland, the Home Office, the Ministry of Education and, last but not least, the Treasury were closely concerned The local-authority associations and the main voluntary bodies had already expressed their general views It might be necessary now to obtain their views on specific details, but time would not be wasted

Welfare of Office Workers

THE Offices Bill was introduced as a private member's measure by Mr Richard Marsh on Dec 11 Although the Government felt that it should not proceed, the second reading was carried[1] The Government have now signified their support by tabling a money resolution authorising an increase in the payments to local authorities to meet the cost of enforcing the measure

QUESTION TIME

Locum Tenens

Mr L A PAVITT asked the Minister of Health if he was aware of the inadequacy of the present arrangements to employ locum tenentes in general practice and the hospital services —Mr WALKER-SMITH replied I am aware that individual difficulties sometimes occur, but I am not clear that action by me would be appropriate Mr PAVITT In view of the fact that so many of these difficulties occur because of the time taken to solve these problems of locum tenentes, will the Minister give consideration to the introduction of a scheme for a local service, and further, will he consider the possibility of using the trainee assistants scheme in order to help in this respect? For example, if the trainee were given two months at the end of his normal training period to enable him to obtain wider experience on a general basis and also in hospitals that would help Will he also consider the possibility of refresher courses for consultants and specialists, so that they may come down into the arena of family doctoring, which might be beneficial to them and help the general practitioner in solving his problem of locums?—Mr WALKER-SMITH On the first of those three points, I doubt whether an organised service of the sort suggested would really meet the case because there are so many and varied personal factors involved in these matters On the second point, I should like to consider the suggestion The third point is very revolutionary in a professional service, and I think that, like Agag of old, I had better tread delicately

Dr EDITH SUMMERSKILL While not asking the Minister to commit himself now, will he reconsider his first answer? As he realises, the great majority of doctors today are employed by the State and find it very difficult to obtain a deputy in case of illness, in fact, there is no certainty that they can obtain a deputy This also applies during holidays We should at least equate doctors with Civil Servants so that deputies who can be relied upon are available. Perhaps the Minister will reconsider the whole matter?—Mr WALKER-SMITH I am always ready to consider further these matters, but I was giving my impression as it now stands We should not exaggerate the difficulties about locums In particular, we have to remember that there has been a considerable increase in the number both of general practitioners and hospital doctors overall These difficulties have to be seen against that more satisfactory background

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[1] See *Lancet*, 1959, ii, 1151

Obituary

FRANK BARNES

M S Lond , LL D Birm , F R C S

Mr Frank Barnes, consulting surgeon to the Birmingham General Hospital, had made many gifts to the United Birmingham Hospitals and the Medical School, and a ward in the Queen Elizabeth Hospital is dedicated to him The postgraduate surgical travelling fellowship he endowed in 1944 has enabled young surgeons to widen their experience by working abroad More recently he gave generously towards the building of the new library at the Medical School which, in recognition of his own and the late Stanley Barnes' distinction and generosity, has been named the Barnes Library Mr Barnes was to have performed the opening ceremony last October but to everyone's sorrow he was too ill to do so He died on Feb 18 at the age of 90

He was born, lived, and worked in Birmingham all his life After qualifying from Mason College, Birmingham, in 1898, he took the degree of M B Lond. two years later He held many resident surgical appointments before being elected to the honorary staff of the Birmingham General Hospital in 1903 He was also consulting surgeon to the Birmingham and Midland Eye Hospital, the Hospital of St. Cross, Rugby, and the Sutton Coldfield Cottage Hospital, and for ten years he was on the staff of the Birmingham Orthopædic and Spinal Hospital (now the Royal Orthopædic Hospital) During the 1914–18 war he served in the R.A.M C

As a teacher he was lucid and orthodox and in the University was lecturer in anatomy and operative surgery He published little and he evaded high office and public recognition, but he served as president of the Midland Medical Society in 1930 In 1957 the University of Birmingham conferred on him the honorary degree of LL D

A G W writes

"Mr Barnes was a surgeon of outstanding ability, combining high diagnostic acumen with superb operative skill and dexterity and these qualities and his quiet, friendly, and unassuming personality made him one of the most sought after surgeons in the Midlands over many years He practised in the days before the increasing diversity and complexity of surgical techniques demanded narrow specialisation and he was essentially a general surgeon, but his major interests were abdominal surgery and neurosurgery He was one of the first surgeons in England to operate successfully on tumours of the spinal cord.

"Although they were not related, Mr Barnes and the late Stanley Barnes were close friends and they spent much of their leisure together fishing, playing golf at Moseley Golf Club, and bridge at the Clef Club Mr Barnes was also a keen

gardener and a connoisseur of wines His death ends a long and happy life of great achievement and distinction, during which his kindness, generosity, and warm nature won him many friends "

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H C S writes

" During the first nine years of Atkey's directorship, the Sudan Medical Service shared in the general development of the country Its work increased fourfold and more of the southern and eastern provinces came under effective medical control Important training schemes were either inaugurated by Atkey or were greatly developed under his inspiration, and the Kitchener School of Medicine for Sudanese students was opened in 1924 It was almost entirely due to Atkey's efforts that money was raised not only to pay for the buildings but also to provide a sum of £E24,000 as a nucleus for an endowment fund By 1931 the effects of the world slump reached the Sudan, and for a time progress in all Government departments ceased Recovery however was rapid and by the time of Atkey's retirement in 1933 expansion had been resumed

" He was a keen horseman and he played polo and tennis with his customary vigour He did not practise after leaving the Sudan but travelled widely, often by air in his own plane with Mrs Atkey as co-pilot This special interest terminated in a crash in central Africa when en route for the Cape During the late war he was employed in organising and inspecting first-aid posts in the London regional area For the last four years he had been in poor health and his activities were seriously curtailed In his own sphere he had played an important role in the Sudan's growing capacity for independence "

RUPERT GEORGE ANDERSON

M D Edin, D P M

Dr R G Anderson, one of the Lord Chancellor's visitors in lunacy, died on Feb 12

He was educated at Glasgow Academy, Loretto School, and Edinburgh University, where he graduated M B in 1924 He joined the London County Council mental service in 1925, and held posts at Long Grove Hospital, Cane Hill Hospital, and Horton Hospital, where he was deputy medical superintendent In 1938 he was appointed a commissioner of the Board of Control and, apart from three years during the late war in the Middle East as a lieut -colonel in the R A M C, he remained with the Board until 1953, when he was made a Lord Chancellor's visitor

W D N writes

" Anderson was a most delightful colleague, loyal and conscientious He was truly loved by both patients and staff He was a good clinician and in his duties as a Chancery visitor he exhibited great tact and shrewdness His courtesy and manner were almost Victorian In many ways he was a born actor and mimic, full of good humour He will be greatly missed by his colleagues and many friends in the provinces "

Dr Anderson is survived by his wife, a son, and two daughters

GILBERT WINTER DRYLAND

M B Cantab

Dr G W Dryland, who died on Feb 3, qualified a Guy's in 1907 Before the first world war he had settle in practice at Kington in Herefordshire where he spen the rest of his life

R E I writes

" Dr Dryland lived life to the full and delighted in it H was a keen nature-lover and antiquarian Kington, lying in th little known border country between England and Wales, wit its rolling hills, its flower lanes, its clouds and sunshine, it meadows fenced with white iron railings, its streams running t the Wye Valley and its half-timbered houses, meant much t him, and he captured its beauty in photographs which adorne his home His garden was as lovely as any I have known He also enjoyed travelling and sailing He was a pionee motorist who owned a car when motoring was still an adventure It always gave him pleasure to recall how his first ca would only climb a certain hill if driven backwards

" Perhaps his most endearing characteristic was a beautifully quiet sense of humour which kept peeping out in all he did It informed a great deal of his writing and made it a joy to receive a letter from him Several Guy's men, of whom I was one, enjoyed doing locums in Kington for him, for to do so was to see country practice at its very best He was sustained by a deep religious faith and was as much beloved for his kindness and gentleness as for his great experience and professional skill "

VASSILI ALEKSEEVICH GILYAROVSKI

Dr Gilyarovski, professor of psychiatry at the Second Moscow University, died last year at the age of 83

Gilyarovski came from a poor family in Southern Russia and began to work for money early when he was still a schoolboy and student, coaching pupils and taking part in anti-epidemic campaigns, in mass-vaccination, and in other social activities among the population He studied under Korsakov, Serbsky, Kozhevnikov, and especially under the physiologist Ssechenov for whom he had a great admiration After serving his apprenticeship in mental hospitals and after some work in neuropathological laboratories, his main interest became the treatment of neurotics and of minor psychiatric abnormalities He did psychiatric work with children and organised speech therapy, was at one time an advocate of the psychoanalytic ideas of Freud in Russia As president of the Society of Psychiatrists and Neuropathologists he took an active part in the extension of the network of psychoneurological clinics in all towns of the Soviet Union, and he drew up rules for these institutions providing full-time care, and day-hospital care, and guardianship He was always much concerned with the practical side of medical work In the early '30s he seems to have conceived the idea of the day hospital as a new type of psychiatric institution

W M -G writes

" From his preference for humanitarian and pathogenetically well-founded therapy methods came his opposition to the extensive use of electro-shock in psychiatry and to leucotomy It may well be that the latter was prohibited in the U S S R on the instigation of Gilyarovski He himself elaborated what he called a physiological method of treatment ' electrosleep ' and wrote a monograph about it This was an electrically induced sleep state, based on Pavlov's idea of the importance of protective inhibition in the cortex Gilyarovski's scientific views were towards his later years very much influenced by Pavlov, who himself provided a comprehensive theory of psychic phenomena on the basis of his physiological concepts of reflex activity Gilyarovski tried to extend and to confirm Pavlov's views, and it may well be that he was one of those responsible for the undisputed prevalence of Pavlovian ideas in modern Russian psychiatry "

Notes and News

PROGRESS IN IMMUNOLOGY

LONG a source of tools indispensable to bacteriology, blood-transfusion, and diagnosis, immunology has latterly become an enlarging area of biological research. Everywhere there is talk of its new facts and new theories, particularly those relating to immunological tolerance and autoimmunity. Perhaps because of their apparent relevance to problems of surgery and medicine, many workers are now concerned with the mechanisms of antibody responses, especially at the cellular level, and their relation to tissue reactions.

An impressive share in the recent advances belongs to the Walter and Eliza Hall Institute, Melbourne, and to its director, Sir Macfarlane Burnet. His annual report on the work of the institute[1] is a reminder of what is being done there on the fundamentals of immunology. Current investigations deal among much else with the production of antibody by single cells, the cellular transfer of antibody-producing capacity and of characteristic responses, and the genesis and regeneration of plasma cells. Work is also in progress on the behaviour of tolerant cells in many situations, on the metabolic activity of lymph-nodes, and on the production of autoimmune disease experimentally by cell transfer. Throughout, the emphasis is on the immunological reactions and relationship of cells and their subcellular components—an approach which keeps the institute well to the fore in biological research. The clinical research unit there provides a medical link with the experiments. Clinical studies in the immunology of, for example, systemic lupus erythematosus, lupoid hepatitis, thyroid disease, and macroglobulinæmia have produced interesting new facts—sometimes puzzling ones.

One of the chief problems of autoimmune disease, whether clinical or experimental, is the relative significance in the disease process of the various antigen-antibody systems which are being discovered. Little headway has yet been made in characterising specific antigens involved in tissue reactions. Progress at the Melbourne institute encourages workers elsewhere in the attempt to define the extent and importance of immunopathology in human disease.

MEDICAL REFERENCES

THE first issue has now appeared of the *Index Medicus*, which is to replace the *Current List of Medical Literature* of the National Library of Medicine of the United States Department of Health and the *Quarterly Cumulative Index Medicus* of the American Medical Association. The new index will be published monthly by the Library, and sold by the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C. ($20 per year, $25 foreign, single copies $2.25). The monthly issues will be collated each year, and an annual *Cumulated Index Medicus* will be sold by the Association.

Postgraduate Medical School of London

At a reception on Feb. 17 at Hammersmith Hospital, the guests were received by Lord Alexander of Tunis, president of the school, and Lord Coleraine, chairman of the school management committee. Lord Alexander spoke of the help the school was receiving from the Dominions, particularly in the matter of the appeal to finance the new buildings. The appeal had started very well in this country, Pakistan and South Africa had contributed generously, and, Lord Alexander added, Canada was able to play her part, now that income-tax difficulties had been overcome, thanks to the generosity of Canada and Lord Coleraine's personal help. Lord Coleraine said that when the extent of Dominion aid was known, it would be decided whether to complete the appeal in this country; the essential was that the buildings should go straight on to completion.

University of Leeds

Mr C. P. Mills has been appointed clinical lecturer in otology, and Mr Verna Wright lecturer in the department of medicine (for rheumatism research).

University of Manchester

Dr Ralston Paterson, lecturer in clinical radiotherapy, has been granted the status of professor, with the title of professor of radiotherapeutics. He will continue to hold his appointment as director of radiotherapy at the Christie Hospital and Holt Radium Institute, Manchester.

Dr Paterson was educated at George Heriot's School, Edinburgh, and the University of Edinburgh, where he graduated M.B. with honours in 1923. After postgraduate study at the University of Cambridge he took the D.M.R.E. in 1924. From 1926 to 1930 he held appointments in Minnesota and Chicago, and in 1930 he was appointed acting director of the radiological department in the Edinburgh Royal Infirmary. The following year he moved to Manchester to take up his present appointment at the Christie Hospital and Holt Radium Institute. He has been a part-time member of the staff of the university since 1942. In 1953 he became honorary director of the Medical Research Council's betatron research unit. He was elected a fellow of the Royal College of Surgeons of England in 1948, and he was appointed C.B.E. in 1950.

The university has instituted a chair of preventive dentistry to which the council has appointed Mr J. L. Hardwick, M.D.S., who has held a readership in dental surgery in the University of Birmingham since 1952.

University of Sheffield

The following appointments have been made:

Dr Margaret M. Platts, lecturer in medicine; Dr H. A. Salmon, assistant lecturer in physiology; Dr J. D. Howard and Dr O. H. Simms, part-time instructors in anæsthetics.

International Symposium on Allergy

This symposium, organised by the European Academy of Allergy in collaboration with the Spanish Society of Allergy, will be held in Barcelona on June 3 and 4. Further particulars may be had from the secretary, Mr Camps, Academia de Ciencias Medicas, Via Layetana 31, Barcelona 3, Spain.

Toxic Sprays Study Group

Dr J. M. Barnes, Dr Donald Hunter, and Prof. W. L. M. Perry have been appointed members of this group which has been set up by the Minister for Science, the Minister of Agriculture, Fisheries, and Food, the Secretary of State for Scotland, and the Minister of Health.

Expenditure on the National Health Service

The Civil Vote on Account for 1960–61 shows estimated net expenditure on the National Health Service as £519,172,485 in England and Wales, compared with £501,124,100 in the present financial year, and as £64,332,850 in Scotland, compared with £61,617,555 in the present year (1960–61, Vote on Account. Civil Estimates. H.M. Stationery Office. 6*d*.)

Social Security Agreements with Denmark and Finland

The reciprocal social security agreements which the United Kingdom concluded last July and August with Finland and Denmark have been ratified, and both will come into force on March 1.

The agreements cover benefits provided by the schemes of national insurance, industrial-injuries insurance, and family allowances in this country and the corresponding benefits in Denmark and Finland.

International Course on Lyophilisation

The Association des Cours Internationaux de Lyophilisation will run a second international course at Lyons from Aug. 29 to Sept. 9. Like the first international course, which was held in 1958, the meeting will be sponsored by the International Institute of Refrigeration and the International Association of the Societies of Microbiology. Teaching will be in English and French and the programme includes lectures, technical demonstrations, and discussions. Dr A. S. Parkes will give the opening lecture. Further particulars may be had from Dr L. R. Rey, Laboratoire de Physiologie, École Normale Superieure, 24, rue Lhomond, Paris, 5e, France.

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[1] 40th annual report (1958-59) of the Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.

A New Veterinary Journal

The rapid advance of veterinary research has led the British Veterinary Association to start a new quarterly journal entitled *Research in Veterinary Science* Contributors and subscribers, at home and overseas, are asked to note that manuscripts should be sent to the scientific editor, 7, Mansfield Street, London, W 1, and annual subscriptions (90*s* for non-members and 60*s* for members) to Blackwell Scientific Publications, Ltd , 24, Broad Street, Oxford

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Mr Derek Walker-Smith, the Minister of Health, has appointed Mr B R Rayner to be his assistant private secretary

A refresher course for general practitioners will be held at Joyce Green Hospital, Dartford, Kent, at 3 P M on Fridays from April 22 to July 1 Further particulars may be had from Dr J C Hogarth, West Hill Hospital, Dartford

The Hospital for Sick Children, Great Ormond Street, London, W C 1, has prepared a brochure, *Welcome to Hospital*, which it is proposed to send to parents when arrangements are being made to admit a small patient

The Royal National Mission to Deep Sea Fishermen sends bundles of magazines aboard vessels before they leave port These are always eagerly read on the voyage no matter what the date A doctor has lately sent a bundle of discards from his waiting-room and the Mission wonders whether others would be willing to follow their colleague's example Bundles should be sent direct to the Mission Institutes R N M D S F , Goulton Street, Hull; or R N M D S F , 4, Charles Street, Milford Haven

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CORRIGENDUM *Polyneuritis and Central Hypertension due to Non-parotitic Mumps* —Dr Pallis asks us to correct the antibody figures given in his paper of Feb 13 They should have been

Date (1959)	*Day of disease*	*Mumps "virus particle" antigen*	*Mumps "soluble" antigen*
Jan 13	6	16	64
" 23	16	64	64
Feb 19	43	32	16
Mar 13	65	<8	8

Diary of the Week

FEB 28 TO MARCH 5

Monday, 29th

UNIVERSITY COLLEGE, Gower Street W C 1
5 P M Dr Antoinette Pirie Biochemistry of the Eye (First of two lectures)
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P M Dr Brian Ackner Modern Drug Treatment of Mental Disorder
UNIVERSITY OF ST ANDREWS
1 P M (Queen's College, Dundee) Dr William Walker, Dr H B Goodall Hypersplenism

Tuesday, 1st

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 30 P M *Pathology* Prof L S Penrose Human Genetics and Disease Dr Hermann Lehmann Familial Deficiency of Pseudo cholinesterase Dr Aron Holzel Galactosæmia—a Hereditary Disease
8 30 P M *Orthopedics* Mr Rainsford Mowlem, Prof C G Rob, Mr R G Pulvertaft Early Management of Soft Tissue Injuries of the Extremities
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr Alick Isaacs Anti viral Action of Interferon
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Mr C W F Burnett Aspects of Abortion
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr Isaac Muende Diagnosis and Treatment of Fungous Infections
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr K I Nissen Mechanism and Treatment of Compression of the Median Nerve at the Wrist
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Mr Wylie McKissock Surgical Versus Medical Treatment of Posterior Communicating Aneurysm
UNIVERSITY OF ST ANDREWS
5 P M (Queen's College, Dundee) Prof Adam Patrick The Plague of Athens, 430 B C —A Problem in Diagnosis

Wednesday, 2nd

UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine) Prof Gerhard Schramm (Tubingen) Mutagenesis in Viruses
ROYAL SOCIETY OF MEDICINE
5 15 P M *History of Medicine* Dr R I Smith George Henry Lewes and his *Physiology of Common Life*, 1859 History of Gastric Surgery
8 P M *Surgery* Dr Keith Simpson, Mr J P Mitchell, M Milstein, Dr J B Wyman, Mr R H F Brain Accidents Operating theatre
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr Fraser Roberts Sex-linked Inheritance in Man
INSTITUTE OF DERMATOLOGY
5 30 P M Mr I F Hughes Mites or Acari
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Mr W P Cleland Surgical Treatment of Fallot's Tetralo
OXFORD UNIVERSITY
5 P M (Radcliffe Infirmary, Oxford) Dr D Denny Brown N Brief Recurrent Cerebrovascular Episodes (Litchfield lec
MIDLAND MEDICAL SOCIETY
8 15 P M (36, Harborne Road, Edgbaston) Prof Douglas H Growth and its Disorders
MEDICO CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P M (18, Nicolson Street, Edinburgh) Prof Stanley A Therapeutic Miscellany
UNIVERSITY OF ST ANDREWS
2 30 P M (Queen's College, Dundee) Dr Walker Current Stu Blood Coagulation

Thursday, 3rd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C
5 30 P M Dr R M B MacKenna Dermatological Aspect of Cer the Diseases of the Mouth and Ear
NUFFIELD ORTHOPAEDIC CENTRE, Wingfield Morris Orthopædic H Oxford
8 30 P M Dr W H Harris Fibrous Dysplasia
UNIVERSITY OF ST ANDREWS
5 P M (Queen's College, Dundee) Prof W D Armstrong (Minnes Studies of Fluoride Metabolism with Radiofluoride

Friday, 4th

ROYAL SOCIETY OF MEDICINE
10 30 A M *Otology* Dr Gunnar Lidén (Gothenburg), Mr M McLay, Mr Gavin Livingstone Measurement of Deafness
2 30 P M *Laryngology* Dr Herman Diamant (Stockholm), S Cameron, Mr D H Patey Salivary Glands—Physiology, logy, and Treatment
5 30 P M *Anæsthetics* Dr J B Riding Postoperative Vomiting
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Sir Eric Riches New Growths of the Kidney
4 P M Dr Roberts Medical Genetics
JAMES YEARSLEY LECTURE
5 P M (1, Wimpole Street, W 1) Mr Ian Thorburn A Critical Rev Tympanoplastic Surgery
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W C 1
4 30 P M Dr Macdonald Critchley History of our Conception as Origin of Language in Man (II)
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W
3 30 P M Dr D A Osborn Blood Diseases in Ear Nose, and T Conditions
MIDLAND CENTRE FOR NEUROSURGERY, Holly Lane, Smethwick, 4
8 P M Professor Denny Brown The Nature of Polymyositis and R Muscular Disease
PLYMOUTH MEDICAL SOCIETY
8 30 P M (Freedom Fields) Mr P D Trevor-Roper Influence Disease on the Artists

Saturday, 5th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
NOON Prof Michel Portmann (Bordeaux) Interposition for Otoscle
MIDLAND THORACIC SOCIETY
3 P M (36, Harborne Road, Edgbaston) Prof W Melville Ar Management of Cardiac Failure

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Appointments

ANKLESARI, R , M B Bombay anæsthetic registrar, United Not Hospitals
GOLDIE RUTH Y , M B St And , D Obst , D P H senior assistant Tottenham and Hornsey, Middlesex
JAYANANDAIAH, H P , M B Mysore, D T M & H medical registrar, I Hospital, Ipswich
KING P F , F R C S , D L O consultant otologist, Lewin Water Reside School for Partially Deaf, Hertfordshire
MILLAR G R , M B Edin M O , Eastern Regional Hospital Board, S land, for duty as deputy group administrative medical superinten County and City of Perth general hospitals
YARROW, ALFRED, M B Edin , D P H area M O , South east Essex, M Benfleet, Canvey Island, Rayleigh, and Rochford
YULE, I G , M B Manc assistant divisional M O , Failsworth Lancashire

Colonial Appointments:

BOYD, P I , M B Lond , M P H principal M O , Jamaica
COLLYMORE, H W M , M B Lond , F R C S specialist M O , Trinida
COMLEY, J P , M B Edin M O , Northern Region Nigeria
COOMBES, A H R , M B , M R C S D P H , D T M & H A D M S H Kong
CRAIG W J A , M B Edin M O , Hong Kong
DAVIES, C W , M R C S , D P H secretary to Ministry of Health D M S , Uganda
HARNARAYAN TIRCHAL, M B Lond , F R C S specialist M O Trinida
HARROWER, J , M B M O , Uganda
HYSLOP, D A , M B Lond M O , Uganda
LEIPER, N K , M B Cantab M O , Uganda
MOORE G W M R C S senior M O , Dominica
NEWLAND M A M B Cantab M O Aden
RATULANGIE C J A M D Utrecht M O , Northern Region, Nigeri
D , M B Cantab , F F A R C S , D A specialist (anæsthet
TENG, PIN HUI, M B Hong Kong , D P H D D M & H S , Hong Kong

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